Updated SPC – 22 Aug 2015

Summary of Product Characteristics

1. **NAME OF THE MEDICINAL PRODUCT**
ROTAVAC® (Rotavirus vaccine (Live Attenuated, Oral) Vero cell-derived

Rotavirus Vaccine (Live Attenuated, Oral) is a monovalent vaccine containing suspension of live rotavirus 116E prepared in Vero cells. Rotaviruses are double-stranded 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® is 0.5 mL containing not less than [NLT] $10^{5.0}$FFU [Focus Forming Unit] of live rotavirus 116E.

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**
List of ingredients and quantities

2.1 Composition of ROTAVAC®

Ingredients	**Quantity/0.5ml**
Rotavirus 116E, Live	NLT $10^{5.0}$ FFU
Potassium Phosphate Monobasic	0.258 mg
Potassium Phosphate Dibasic	0.625 mg
Sucrose	37.31 mg
Potassium L-Glutamate Monohydrate	1.0 mg
Neomycin Sulphate	15 ug
Kanamycin Sulphate	15 ug
Dulbecco's Modified Eagle's Medium (DMEM)	4.4 mg
Water for Injection (WFI)	qs

pH is in the range of 7.2 to 8.0

3. **PHARMACEUTICAL FORM**
ROTAVAC® is 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.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications
For prophylactic use only.
ROTAVAC® is indicated for active immunisation 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. Dosage 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 immunisations 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 immunisations are initiated later than 6 weeks of age and/or at a longer dose interval than 4-weeks, ROTAVAC® should 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 vaccines 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**.

In case of multi-dose vial, care should be taken not to contaminate the multi-dose dropper of the vaccine with saliva of the babies. Unopened vaccine vials are stable for 6 months when stored at 5°C ±3°C any time during the shelf-life. Once opened, multi-dose vials should be kept at 5°C ±3°C.

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 immediate spitting or vomiting is <0.5%.

*Physician's discretion is advised.

4.3. 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).

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 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®, 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 vaccines 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 of 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]. Of the 22 G9P[11] cases, 15 were classified as mild severity (Vesikari score <7) and 7 were classified as moderate severity (Vesikari score 7-10).

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.

4.5. Interaction with other medicinal products/active immunising agents 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 immunisation titres 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 DTP, 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.

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. Effects on ability to drive and use machines

Not Applicable.

4.8. Adverse Events

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 initial two phase I studies of Oral Rotavirus Vaccine (ORV) 116E conducted in healthy adults and children in the USA there were so safety concerns. There was one case of fever and two cases of diarrhoea in the adult 116E vaccine recipients. Similarly, one case of fever and two cases of diarrhoea were reported in the child 116E vaccine recipients.

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 6-7 weeks of age, incidence 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 events 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 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.

Solicited and Unsolicited Adverse Events

Solicited and unsolicited adverse events were obtained via contact with the parents or guardians during the 14-day period following each administration of ROTAVAC®. This data on adverse events was collected through twice daily home visits by the study staff during the 14-day follow up period.

In the phase Ia/IIb trial, the most frequently reported expected solicited adverse events were fever, diarrhea, and vomiting. Other unexpected adverse events recorded during this period include cough, runny nose, irritability and rash. There were no significant differences in the reporting or severity of adverse events among recipients of ROTAVAC® and recipients of placebo.

Laboratory toxicity evaluated in a subset of participants 4 weeks after the first administration of the test article did not show any significant differences in the laboratory parameters estimated or in the severity of the laboratory toxicity between the vaccine and placebo groups for either dosage.

In the larger phase III trial, immediate IAEs are reported separately and the incidence was low (<0.5%) and similar across both vaccine and placebo recipients. Vomiting and infantile spitting is commonest reported symptom (0.3% and 0.1% respectively).

Solicited adverse events include fever, diarrhea, vomiting, cough, runny nose, irritability and rash. In the phase III trial, no differences were observed in post vaccine reactogenicity events in ROTAVAC® and placebo groups.

Adverse events reported at a frequency of 1% or greater in the Phase III trial are summarized in the table below:

Table 1. Subjects with Adverse Events Reported at a Frequency of 1% or greater in either group, within 14 days ROTAVAC®/placebo administration - all three doses combined.

Primary SOC Preferred Term	**ROTAVAC® (N=1530) n (%) No. of Events**	**Placebo (N=768) n (%) No. of Events**	**Total (N=2298) n (%) No. of Events**	**p-value**
At Least One Follow-up AE	1424 (93.1%) 8461	719 (93.6%) 4298	2143 (93.3%) 12759	0.66
General Disorders And Administration Site Conditions	**1299 (84.9%) 4953**	**657 (85.5%) 2508**	**1956 (85.1%) 7461**	**0.71**
Pyrexia	1251 (81.8%)	635 (82.7%)	1886 (82.1%) 6573	0.60

	4349	2224		
Irritability	268 (17.5%) 367	131 (17.1%) 176	399 (17.4%) 543	0.82
Local reaction	65 (4.2%) 83	32 (4.2%) 39	97 (4.2%) 122	1.00
Crying	68 (4.4%) 77	25 (3.3%) 26	93 (4.0%) 103	0.18
Sluggishness	37 (2.4%) 42	26 (3.4%) 27	63 (2.7%) 69	0.18
Respiratory, thoracic and mediastinal disorders	**844 (55.2%) 2144**	**431 (56.1%) 1098**	**1275 (55.5%) 3242**	**0.69**
Cough	627 (41.0%) 1136	322 (41.9%) 597	949 (41.3%) 1733	0.69
Rhinorrhoea	572 (37.4%) 932	286 (37.2%) 452	858 (37.3%) 1384	0.96
Nasal congestion	50 (3.3%) 62	23 (3.0%) 43	73 (3.2%) 105	0.80
Gastrointestinal disorders	**505 (33.0%) 841**	**226 (29.4%) 410**	**731 (31.8%) 1251**	**0.09**
Diarrhoea	361 (23.6%) 529	168 (21.9%) 254	529 (23.0%) 783	0.37
Vomiting	174 (11.4%) 243	83 (10.8%) 122	257 (11.2%) 365	0.73
Haematochezia	17 (1.1%) 17	10 (1.3%) 12	27 (1.2%) 29	0.69
Constipation	14 (0.9%) 17	9 (1.2%) 9	23 (1.0%) 26	0.66
Skin and subcutaneous tissue disorders	**133 (8.7%) 174**	**79 (10.3%) 102**	**212 (9.2%) 276**	**0.22**
Rash	124 (8.1%) 161	72 (9.4%) 93	196 (8.5%) 254	0.30
Infections and infestations	**105 (6.9%) 149**	**58 (7.6%) 87**	**163 (7.1%) 236**	**0.55**
Nasopharyngitis	86 (5.6%) 121	45 (5.9%) 70	131 (5.7%) 191	0.85
Metabolism and nutrition disorders	**79 (5.2%) 94**	**42 (5.5%) 46**	**121 (5.3%) 140**	**0.77**
Decreased appetite	79 (5.2%) 94	42 (5.5%) 46	121 (5.3%) 140	0.77
Eye disorders	**41 (2.7%) 56**	**20 (2.6%) 22**	**61 (2.7%) 78**	**1.00**
Conjunctivitis	25 (1.6%) 36	13 (1.7%) 13	38 (1.7%) 49	1.00
Ear and labyrinth disorders	**17 (1.1%) 20**	**9 (1.2%) 9**	**26 (1.1%) 29**	**1.00**
Otorrhoea	14 (0.9%) 17	8 (1.0%) 8	22 (1.0%) 25	0.82

Restricted to those events occurring in at least 1% of subjects in either group and includes SAEs reported during this 2 week period**.** n= Number of Subjects in the Category. N= total Number of Subjects in Each Treatment Group in the Detailed Safety Follow-Up Subset. p-value: Calculated using Fisher's Exact test where the total number of subjects with at least one event per treatment group is > 5. SOC = System Organ Class; PT = Preferred Term; AEs are coded using MedDRA Version 16.0

Serious Adverse Events

No vaccine-related SAEs were reported in the phase Ib/IIa trial. A total of 15 SAEs were reported in this trial in 13 subjects in the two vaccine cohorts. All of these were considered as remotely related or unrelated to vaccination.

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.

The most frequently reported serious adverse events included gastroenteritis and lower respiratory tract infection (including bronchopneumonia). There were no differences in the reports of serious adverse events among recipients of ROTAVAC® and recipients of placebo, with the exception of reports of gastroenteritis associated with rotavirus infection; there were significantly more reports of rotavirus gastroenteritis among infants receiving placebo, consistent with the demonstrated efficacy of ROTAVAC® against severe rotavirus gastroenteritis.

Deaths

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 4531 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. The occurrence of deaths is spread throughout the follow-up period of the trial without any clustering after vaccine doses.

Intussusception

In both trials, all enrolled subjects were monitored for any signs and symptoms of suspected IS throughout the trial. The subject was assessed at home/study clinic, by a physician clinical coordinator and findings confirmed by a pediatrician. If the parents reported to the study physician or the subjects were found by physicians to have any of the following: blood in stools, palpable abdominal lump, continuous vomiting, inconsolable crying (this was not a criterion in the phase III clinical trial but only in phase Ib/IIa clinical trial), or abdominal distension, the subject was transported to a hospital for ultrasonography. All cases of IS were reviewed by an independent IS Committee, who determined whether the case met the Diagnostic Certainty Level 1 criteria developed by the Brighton Collaboration Intussusception Working Group.

No cases of intussusception were observed in the phase Ib/IIa trial. In the phase III trial, there were eight confirmed cases of intussusception observed among the 4,532 recipients of ROTAVAC® (0.2%), and three among the 2,267 recipients of placebo (0.1%). The minor difference in number of subjects with intussusception was not statistically significant. There were no reports of IS during the vaccination period; the first case occurred in a placebo subject 36 days after the third dose. The first case reported among recipients of ROTAVAC® occurred 112 days after the third vaccination. All intussusception events were resolved after pneumatic reduction or barium enema; none required surgical intervention and none was fatal.

Rotavirus Gastroenteritis where the Genotype of the Vaccine Strain, G9P[11] was detected

In the phase III trial rotavirus gastroenteritis associated with G9P[11]was identified only among recipients of ROTAVAC® and was noted after the first dose and prior to the third dose, suggesting that the G9P[11] was vaccine virus rather than wild virus. Twenty-two G9P[11] rotavirus gastroenteritis cases occurred following 13296 administrations of ROTAVAC® (approximately 1 event in 600 doses for any dose and approximately one in 200 for the first dose); all occurred in the ROTAVAC® group, 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]. Of the 22 G9P[11] rotavirus gastroenteritis cases, 15 were classified as mild severity (Vesikari score <7) and 7 were classified as moderate severity (Vesikari score 7-10). There are two possible explanations for these findings: the vaccine causes rare, and mostly mild gastroenteritis; or shedding of ROTAVAC® was detected during gastroenteritis cases caused by other non-identified pathogens.

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

5.1. Pharmacodynamic properties

Mechanism of Action

Protection against rotavirus infection is mediated by both humoral and cellular components of the immune system. The exact mechanism by which rotavirus vaccines protects against rotavirus gastroenteritis is unknown.

Clinical Efficacy

A multi center phase III clinical trial was conducted in India to evaluate the efficacy of ROTAVAC® against severe rotavirus gastroenteritis.

The very close monitoring of subjects in this large trial optimized identification, characterization and severity-scoring of cases of gastroenteritis. For the primary endpoint analysis (follow-up through 24 months of age), ROTAVAC® prevented 55.1% (95% CI: 39.9, 66.4) of cases of severe non-vaccine rotavirus gastroenteritis in the per protocol population. This efficacy was demonstrated across a broad array of rotavirus genotypes circulating in India (G2P[4], G1P[8], G12P[6] and G12P[8] were the most common genotypes). Efficacy was also demonstrated against non-vaccine rotavirus gastroenteritis of any severity (VE= 36.4% [95% CI: 26.0, 45.3]). Among very severe cases of non-vaccine rotavirus gastroenteritis, the vaccine efficacy was 57.2% (95% CI: 0.3, 81.9), although few cases of very severe non-vaccine rotavirus gastroenteritis occurred.

Table 2. Efficacy Analysis by Genotype

	n(%) ROTAVAC® N= 4354	**n (%) Placebo** N= 2187	**VE (%)**	**CI**
All[1]	93 (2.1%)	102 (4.7%)	55.1%	(39.9, 66.4)
G1P[8]	40 (0.9%)	34 (1.6%)	42.0%	(5.6, 64.2)
G2P[4]	26 (0.6%)	35 (1.6%)	63.4%	(37.4, 78.8)
G12P[6]	8 (0.2%)	13 (0.6%)	69.7%	(21.1, 89.1)
G12P[8]	5 (0.1%)	8 (0.4%)	69.2%	(-6.8, 92.1)
G9P[4]	9 (0.2%)	1 (0.0%)	-343.5%	(-19562, 38.5)
Others[2]	8 (0.2%)	12 (0.5%)	67.1%	(12.6, 88.4)

[1]Total number of subjects included in the PP population is 195; 4 subjects had more than 1 episode of severe non vaccine RV GE and therefore the total number of episodes 199 is greater than the total number of subjects

[2]Includes all genotypes causing 7 cases or less (G9P[8], G1P[4], G1P[6], G2P[6], G1P[0], G0P[0], G9P[0], G12P[11]).
n is the number of subjects in each category.

Efficacy analyses during the first year of life (Table 3) are important since the majority of cases of severe rotavirus gastroenteritis occur during this timeframe. Efficacy analyses during the first year of life demonstrated support for the primary analysis, with efficacy against severe non-vaccine rotavirus gastroenteritis (VE= 56.3% [95% CI: 36.7, 69.9]). Efficacy against non-vaccine rotavirus gastroenteritis of any severity (VE=35.0% [95% CI: 20.2, 46.9]) was also observed. In the limited number of subjects with very severe non-vaccine rotavirus gastroenteritis, the efficacy was 49.8% (95% CI: -42.6, 82.4). ROTAVAC® prevented 53.2% (95% CI: 27.9, 69.7) of all hospitalization ≥ 24hrs due to severe non-vaccine rotavirus gastroenteritis.

Table 3. Efficacy Summary for All Endpoints for Subjects up to 1 Year of Age in the per Protocol Population

	n (ROTAVAC® N= 4354)	**n (Placebo** N= 2187)	**VE**	**CI**	**p Value**
Severe non-vaccine RV GE					
	57	65	56.3	(36.7, 69.9)	<0.0001
Non-vaccine RV GE of any severity					
	226	172	35.0	(20.2, 46.9)	<0.0001
GE of any etiology and severity					
	2065	1019	-2.0	(-10.0, 5.5)	0.6277
Severe GE of any etiology					
	223	147	24.5	(6.3, 38.9)	0.0104
Non-vaccine RV GE of any severity requiring hospitalization or supervised rehydration therapy					
	218	162	33.3	(17.8, 45.8)	0.0001
Severe non-vaccine RV GE requiring hospitalization or supervised rehydration therapy					
	57	65	56.3	(36.7, 69.9)	<0.0001
Severe GE of any etiology requiring hospitalization or supervised rehydration therapy					
	222	146	24.3	(6.0, 38.8)	0.0113
GE requiring hospitalization or supervised rehydration therapy regardless of etiology or severity					
	1933	957	-1.5	(-9.8, 6.1)	0.7208
Very Severe non-vaccine RV GE					
	9	9	49.8	(-42.6, 82.4)	0.2176
Severe Non-vaccine RV GE requiring hospitalization for ≥24 hr					
	44	47	53.2	(27.9, 69.7)	0.0005
Severe Non-vaccine RV GE requiring hospitalization for ≥6 hr					
	47	50	53.0	(28.6, 69.2)	0.0003

n = Number of subjects in the category. Number of Episodes: all reports of GE for the number of subjects in each category N = Total number of subjects in each treatment group. Severe GE Episode: Subjects with a Total Vesikari Score ≥ 11. Very Severe GE Episode: Subjects with a Total Vesikari Score ≥ 16. Non-vaccine RV GE Episode: all genotypes except G9P[11]
Per Protocol: Subjects who received all three doses of ROTAVAC®/Placebo within the prescribed windows and follow up period defined as the period starting on day 15 relative to dose 3

The efficacy of ROTAVAC® against severe non-vaccine rotavirus gastroenteritis in the second

year of life was 48.9% (95% CI: 17.4, 68.4). Efficacy was also maintained in the second year of life against non-vaccine rotavirus gastroenteritis of any severity (VE = 36.2% [95% CI: 20.5, 48.7]).

All efficacy analyses in the Intent To Treat (ITT) population were consistent with the analyses in the per-protocol population.

While comparison across Rotavirus vaccine trials is difficult due to various factors, the efficacy of ROTAVAC® in the first year and second year of life compares favorably with that seen for Rotarix® and RotaTeq® when evaluated in the developing world.

Immunogenicity

A relationship between antibody responses to Rotavirus vaccines and protection against Rotavirus gastroenteritis has not been established.

The immunogenicity of ROTAVAC® was assessed by serum anti-rotavirus IgA ELISA. In the phase Ib/IIa trial a seroresponse was seen in 89.7% of ROTAVAC® recipients (compared to 28.1% of placebo recipients). In the phase III trial a seroresponse was observed in 40.3% of ROTAVAC® recipients and 18.4% of placebo recipients.

In the phase III trial, ROTAVAC® or placebo was administered concomitantly with UIP vaccines, including Oral Polio Vaccine (OPV), and the impact of ROTAVAC® on the immune responses to was evaluated.

Over 99% of subjects received OPV concomitantly with all three doses of ROTAVAC® or placebo. In addition most subjects received a birth dose of OPV prior to enrollment. Many subjects received additional doses of OPV during routine polio vaccination campaigns. The evaluation of the immune responses to the 3 OPV serotypes was performed by measuring geometric mean titers (GMTs) and proportions of subjects meeting the accepted protective titer (neutralizing antibody ≥ 8) for recipients of OPV plus ROTAVAC® (N=262) and OPV plus placebo (N=123). The analyses revealed that subjects receiving OPV plus ROTAVAC® generated immune responses to all 3 polio serotypes comparable to those receiving OPV plus placebo. These data support the concurrent administration of ROTAVAC® and OPV in infants.

Shedding

In both clinical trials, shedding of the vaccine strain, G9P[11], was evaluated during the first week following each administration. Shedding of ROTAVAC® is it ROTAVAC or Rotavirus 116Ewas examined in all the participants in the phase Ib/IIa trial and in the same subset of subjects evaluated for immunogenicity in the phase III trial.

In the phase Ib/IIa trial, shedding was also evaluated on day 28 following each administration.

In the phase Ib/IIa trial shedding was detected in approximately 13% of subjects receiving ROTAVAC®; shedding occurred only during the first week and only following the first administration. A single placebo recipient shed G9P[11] on day 28 following the first administration. G9P[11] shedding was not detectable after the second or third dose, in any of the subjects receiving ROTAVAC® or placebo.

In the phase III trial, G9P[11] was shed in 12.2% recipients of ROTAVAC ®after the first dose, 2.0% after the second and 1.3% after the third dose. Among recipients of placebo, one subject shed this strain after the first dose and one subject shed the strain after the second dose, but no

recipient of placebo shed G9P[11] after the third dose.

These data suggest that there is low risk of fecal-oral transmission of the vaccine strain following vaccination.

5.2. Pharmacokinetic properties

Not Applicable

5.3. Preclinical safety data

A 28 day repeated dose non-clinical toxicity study on oral Rotavirus vaccine 116E live attenuated 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 attenuated candidate vaccine is safe and induced no toxicity in rats and rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Table 4: List of excipients

S No	Excipient
1	Sucrose
2	Potassium Phosphate monobasic
3	Potassium Phosphate dibasic
4	Potassium L-Glutamate, monohydrate
5	Kanamycin Sulphate
6	Neomycin Sulphate
7	DMEM

6.2. Incompatibilities

This product may not be mixed with other medicinal products/active immunising agents.

6.3. Shelf life

ROTAVAC®: 60 months from the date of manufacture. The expiry date of the vaccine is indicated on the label and packaging.

Special precautions for storage

ROTAVAC® is potent when stored at -20°C-till the expiry date indicated on the vial. It can be stored for up to six months at 5°C ± 3°C at any time during shelf life.

Transport conditions

The vaccine can be transported at 5°C ± 3°C using -20°C frozen gel packs.

6.4. Nature and contents of container

Primary packaging materials for 0.5 mL x 1-dose, 5-dose and 10-dose ORV are sterile glass vials, rubber stoppers, tear-down seals and droppers.

Glass vial: 2 mL, 3 mL and 5ml capacity glass vials of USP Type 1 grade are used.
Rubber stopper: 13 mm and 20 mm siliconized and ready for use Grey bromobutyl rubber stoppers are used.
Flip-off seal: Flip-off aluminium seals are used.
Dropper: Gamma-irradiated semi-transparent low density polyethylene moulded dropper to deliver 0.5 mL in 5 drops are used.

6.5. Special precautions for disposal

No special requirements.

Any unused product or waste material shall be disposed of in accordance with regulatory requirements and Material Safety Data Sheet.

7. **MARKETING AUTHORISATION/PREQUALIFICATION/HOLDER**

Manufacturing permission vide No.MF-192/2013, dated 03-09-2013 from Drugs Controller General (I), New Delhi

8. MARKETING/AUTHORISATION NUMBER(S)

Approval vide L.Dist.No.14279/M3B/2013, dated 20-01-2014 as additional product to the license No.03/HD/AP/98/V/R, dated 14.10.1998 valid upto 31.12.2016 for Oral Rotavirus Vaccine 116 E, Live Attenuated from Drugs Control Administration, Hyderabad

Approval vide L.Dis.No.3634/E (V)/TS/2015, dated 25.03.2015 as Amendment to the license No. 03/HD/AP/98/V/R, dated 14.10.1998 valid upto 31.12.2016 for Oral Rotavirus Vaccine 116E Live, Attenuated from Department of Drugs Control Administration, Hyderabad.

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

20-01-2014 for Oral Rotavirus vaccine