LOCAL PRODUCT CIRCULAR S-LPC-V260-OS-082025

Solution for Oral Administration

RotaTeq®

(rotavirus vaccine, live, oral, pentavalent, MSD)

I. THERAPEUTIC CLASS

RotaTeq is a live, oral pentavalent vaccine which protects against rotavirus gastroenteritis.

II. COMPOSITION

IIa. Active Ingredients

Each 2 mL dose contains the following human-bovine rotavirus reassortants: G1, G2, G3, G4, and P1[8]. The minimum dose levels of the reassortants are as follows:

G1 2.2×10^6 infectious units

G2 2.8×10^6 infectious units

G3 2.2×10^6 infectious units

G4 2.0×10^6 infectious units

P1[8] 2.3×10^6 infectious units

The reassortants are propagated in Vero cells using standard tissue culture techniques in the absence of antifungal agents.

IIb. Inactive Ingredients

The reassortants are suspended in a buffered stabilizer solution. Each vaccine dose contains sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80 and also culture media. There are no preservatives or thimerosal present.

III. CLINICAL PHARMACOLOGY

Rotavirus is the leading cause of severe acute gastroenteritis in infants and young children in industrialized and developing countries. Rotavirus gastroenteritis is a universal disease affecting over 95% of infants and young children by the time they are 5 years old, regardless of their socioeconomic status or environmental conditions. Worldwide it is estimated that 138 million children develop rotavirus gastroenteritis each year which results in 25 million clinic visits, 2.1 million hospitalizations and 352,000 to 592,000 deaths. In the US it is estimated that 3.5 million children develop rotavirus gastroenteritis each year which results in 500,000 physician office visits, 55,000 hospitalizations, and 20 to 102 deaths. One out of every 8 children will seek care from a physician and one out of every 73 children will be hospitalized for rotavirus gastroenteritis in the US by the time they are 5 years old. The greatest proportion of hospitalizations occurs among infants and young children between 6 months and 24 months of age. If left untreated without prompt oral or intravenous administration of fluids, rotavirus gastroenteritis may cause dehydration that is fatal.

Rotavirus gastroenteritis is a seasonal illness in temperate climates with epidemics occurring in the winter months. Rotavirus gastroenteritis is generally endemic in tropical and subtropical climates. Rotavirus is responsible for approximately 28% to 71% of all hospitalizations for diarrhea worldwide, regardless of geographic region and season.

Mechanism of Action

Protection from natural rotavirus infection is largely serotype specific. The human rotavirus serotypes (G1, G2, G3, G4, and P1[8]) have been selected for RotaTeq because these strains caused nearly 90% of rotavirus disease in the United States from 1996-1999 and over 88% of rotavirus disease worldwide between 1973 and 2003. The exact immunologic mechanism by which RotaTeq protects against rotavirus gastroenteritis is unknown. Studies suggest a combination of factors is important in rotavirus immunity including neutralizing antibodies to the outer capsid G proteins, serum and secretory IgA, and other local mucosal responses (see *Immunogenicity*).

Efficacy

Overall, 71,942 infants were randomized worldwide in 3 placebo-controlled phase III studies. The data demonstrating the efficacy of RotaTeq in preventing rotavirus gastroenteritis come from 6,983 of these infants from the US (including Navajo and White Mountain Apache Nations) and Finland who were enrolled in 2 of these studies: the Rotavirus Efficacy and Safety Trial (REST) and Study 007. The efficacy evaluations in these studies included: 1) Efficacy against any severity of rotavirus gastroenteritis and 2) Efficacy against severe rotavirus gastroenteritis (see Table 1). The effect on health care contacts for rotavirus gastroenteritis, including hospitalizations and emergency department visits, was also evaluated among the 68,038 infants enrolled in REST and in a subset of 20,736 infants in the Extension study among the Finnish cohort of REST. The infants were followed for up to 2 years in REST and those in the Extension study continued to be followed for up to 3 years post-vaccination. No safety data were collected during the Extension study. The reductions in routine visits to a physician and parent/legal guardian work loss days were also evaluated in REST. The first dose was administered between 6 and 12 weeks of age and subsequent doses were to be given at 4- to 10-week intervals. The third dose was administered to infants as old as 32 weeks of age. Breast-feeding and concomitant administration of other licensed childhood vaccines except for oral poliovirus vaccine (OPV) were permitted in these studies.

As Table 1 shows, RotaTeq was efficacious against rotavirus gastroenteritis of any severity and severe rotavirus gastroenteritis. The efficacy analyses include cases that occurred at least 14 days after the third dose. Severe gastroenteritis is defined as a numerical score of >16 points on a 24-point scale. The scoring system evaluates the clinical manifestations of rotavirus gastroenteritis taking into account the duration and intensity of fever, vomiting, diarrhea, and behavioral changes. The scoring system has been validated to correlate with physician-assessment of the intensity of these signs and symptoms.

Efficacy through the first rotavirus season after vaccination against severe rotavirus gastroenteritis caused by naturally occurring rotavirus of the composite of the G serotypes included in the vaccine (G1-G4) was 98.2%, and efficacy against any severity of rotavirus

gastroenteritis was 73.8%. The vaccine was specifically designed to prevent rotavirus gastroenteritis caused by the individual G-serotypes included in the vaccine (G1, G2, G3, and G4); P1[8] was included in the vaccine to potentially provide cross-protection against non-vaccine G-serotypes that may contain P1[8]. Based on limited data, the efficacy against any severity of gastroenteritis caused by the non-vaccine G serotype (G9) was 74.1%. Efficacy of RotaTeq against rotavirus gastroenteritis by G-serotype is shown in Table 1.

Table 1

Efficacy of RotaTeq against rotavirus gastroenteritis of any severity and severe rotavirus gastroenteritis through the first full rotavirus season after completion of vaccination by G-serotype

Serotype	Number of cases / Number of evaluable subjects		% Efficacy (95% CI)
	RotaTeq	Placebo	
Any Severity			
G1-G4	97/2,758	369/2,869	73.8% (67.2, 79.3)
G1	85/2,757	339/2,860	75.0% (68.2, 80.5)
G2	6/2,755	17/2,856	63.4% (2.7, 88.2)
G3	3/2,754	7/2,850	55.6% (<0, 92.6)
G4	3/2,754	6/2,850	48.1% (<0, 91.6)
G9	1/2,754	4/2,849	74.1% (<0, 99.5)
Severe			
G1-G4	1/2,747	57/2,834	98.2 (89.6, 100)

Infants with Hospitalizations, Emergency Department Visits, and Non-urgent Visits

RotaTeq reduced the rate of hospitalizations, emergency department visits, non-urgent care visits, and parent/legal guardian work loss days. The reduction in hospitalizations and emergency department visits for rotavirus gastroenteritis caused by serotypes G1-G4 was evaluated among 68,038 infants in REST and in a subset of 20,736 infants in the Extension study among the Finnish cohort of REST. The infants were followed for up to 2 years in REST and those in the Extension study continued to be followed for up to 3 years

post-vaccination. During year 3 (RotaTeq n=3,112 infants, placebo n=3,126 infants), there were no health care contacts for rotavirus gastroenteritis in the vaccine group and there was 1 (non-typeable) in the placebo group. Non-urgent care visits and parent/legal guardian work loss days were evaluated for up to two years after vaccination in REST. The rate reductions for health care contacts are shown in Table 2.

Table 2

Number of health care contacts and rate reductions for rotavirus gastroenteritis caused by the G-serotypes included in the vaccine in REST and the Extension study combined

Type of Health Care Contact	RotaTeq	Placebo	% Rate Reduction (95% CI)
Combined Endpoint (Hospitalizations and Emergency Department Visits)*	28	493	94.4 (91.6, 96.2)
Hospitalizations	13	226	94.3 (89.9, 97.0)
Emergency Department Visits	15	267	94.4 (90.5, 96.9)
Non-Urgent Visits**	13	98	86.0 (73.9, 92.5)

*N=68,038 infants vaccinated, follow-up for up to 2 years in REST and for up to 3 years in the Extension study. There were no typeable episodes of rotavirus gastroenteritis leading to hospitalizations or emergency department visits for rotavirus gastroenteritis in year 3.

**N=5,673 infants vaccinated, follow-up for up to 2 years in REST

Among the parents/guardians of the 68,038 infants studied for up to 2 years in REST, there was an 86.6% reduction in work loss days, with 65 work loss days among parents/guardians of recipients of RotaTeq recipients compared with 487 work loss days among parents/guardians of placebo recipients.

The reduction in hospitalizations and emergency department visits for rotavirus gastroenteritis by serotype identified in stool in REST and the Extension is shown in Table 3.

Table 3

Reduction in the numbers of hospitalizations and/or emergency department visits by G-serotype in stool for up to 2 years after vaccination in REST and for up to 3 years post-vaccination in the Extension study*

Serotype	RotaTeq (N=34,035)	Placebo (N=34,003)	Percent Rate Reduction (95% CI)
Number of hospitalizations and/or emergency department visits			
G1	20	440	95.5 (92.8, 97.2)
G2	2	11	81.9 (16.1, 98.0)
G3	2	18	89.0 (53.3, 98.7)
G4	4	24	83.4 (51.2, 95.8)
G9	1	17	94.2 (62.2, 99.9)

* There were no typeable episodes of rotavirus gastroenteritis leading to hospitalizations or emergency department visits for rotavirus gastroenteritis in year 3.

Efficacy between Doses

The protective efficacy of RotaTeq against the incidence of rotavirus gastroenteritis of any severity caused by serotypes G1-G4 in the intervals between doses was not statistically significant. This was evaluated in a post hoc analysis of data from the clinical efficacy cohort of REST (n=5,673 infants).

The protective efficacy of RotaTeq as measured by a reduction in the rate of hospitalizations and emergency department visits for rotavirus gastroenteritis caused by serotypes G1-G4 in the intervals between doses during administration of the 3-dose vaccination series was evaluated in post hoc analyses of data from REST (n=68,038 infants). The results of these analyses are presented in Table 4.

Table 4

Reduction in hospitalizations and emergency department visits for rotavirus gastroenteritis in the intervals between doses during administration of the 3-dose vaccination series in REST

	RotaTeq n=34,035 infants; Placebo n=34,003 infants	
	From ≥14 days after dose 1 until dose 2	From 14 ≥days after dose 2 until dose 3
Serotype	G1-G4	G1-G4
Efficacy estimate % and [95% confidence interval]	100 [72.2, 100]	90.9 [62.9, 99.0]

Efficacy through Multiple Rotavirus Seasons

The efficacy of RotaTeq persisted through the second rotavirus season after vaccination. Among a subset of 4,451 infants who were evaluated, efficacy against any severity of rotavirus gastroenteritis caused by the composite of the vaccine G-serotypes through two seasons after vaccination was 71.3%. The efficacy of RotaTeq in preventing cases occurring only during the second rotavirus season post-vaccination was 62.6% (see Table 5). The efficacy of RotaTeq beyond the second season post-vaccination was not evaluated.

Table 5

Efficacy of RotaTeq against any severity of rotavirus gastroenteritis caused by the G-serotypes included in the vaccine for the second rotavirus season after vaccination.

	RotaTeq	Placebo	% Efficacy (95% CI)
Number of cases / Number of evaluable subjects			
Rotavirus gastroenteritis cases occurring through the first and second seasons	118/2,173	403/2,278	71.3 (64.7, 76.9)
Rotavirus gastroenteritis cases occurring during the second season only	36/813	88/756	62.6 (44.3, 75.4)

Safety and Efficacy in Pre-term Infants

RotaTeq was generally well tolerated and prevented rotavirus gastroenteritis in infants born prematurely. RotaTeq or placebo was administered to 2,070 pre-term infants (25 to 36 weeks gestational age) according to their chronological age in a placebo-controlled study. In a subset of 204 vaccinated infants (99 in the vaccine group), protective efficacy, as measured by a reduction in the incidence of rotavirus gastroenteritis of any severity caused by vaccine serotypes (G1-G4) that occurred at least 14 days after the third dose of vaccine through the first full rotavirus season after vaccination, was 70.3 % [95 % CI <0, 94.7]. In 2,070 vaccinated infants (1,007 in the vaccine group) in REST, protective efficacy, as measured by a reduction in the rate of hospitalizations and emergency department visits for rotavirus gastroenteritis caused by G1-G4 from 14 days for up to 2 years after the third dose, was 100% [95 % CI 74, 100] (see Table 6). Likewise, the protective efficacy, as measured by a reduction in the rate of hospitalizations and emergency department visits for rotavirus gastroenteritis caused by any serotype from 14 days for up to 2 years after the third dose, was 100% [95% CI 82, 100]

Table 6

Efficacy of RotaTeq in pre-term infants

Reduction in incidence of rotavirus gastroenteritis of any severity caused by the vaccine serotypes G1-G4 through one full season post-vaccination in REST		
RotaTeq	Placebo	% Efficacy
Number of cases / Number of evaluable subjects		
3/75	10/78	70.3
Reduction in hospitalizations and emergency department visits for rotavirus gastroenteritis caused by the serotypes G1-G4 for up to 2 years post-vaccination in REST		
RotaTeq	Placebo	% Rate Reduction
Number of hospitalizations and emergency department visits / Number of evaluable subjects		
0/764	15/817	100

Effectiveness

The results of the three post-licensure vaccine effectiveness studies presented in Table 7 demonstrated high and consistent reduction in rotavirus-related or all-cause gastroenteritis hospitalizations, emergency department visits and office visits. These vaccine effectiveness data from the US and France also showed that RotaTeq provided strain specific effectiveness against G12P[8] and sustained protection against rotavirus-related hospitalizations and emergency department visits in children up to the 7th year of life.

Table 7

Post-Marketing Studies Demonstrating the Effectiveness of RotaTeq to Prevent Gastroenteritis

Study design (Region)	Study population	Endpoints	Effectiveness % [95%CI]	RV seasons
Claims database	33,140 vaccinated	Hospitalization and Emergency	100% [87,100]	2007-2008

analysis (US)*	26,167 unvaccinated Aged ≥7 months Received 3 doses	Department (ED) visits due to RVGE† Outpatient visits due to RVGE Hospitalization and ED visits due to all-cause gastroenteritis	 96% [76,100] 59% [47,68]	
Cohort study (France)‡	1,895 vaccinated with 3 doses 2,102 unvaccinated Aged <2 years	Hospitalization due to RVGE	98% [83,100]	2007-2008 2008-2009
Case-control study (US)§	402 cases 2,559 controls¶ Aged <8 years Received 3 doses	Hospitalization and ED visits due to RVGE *Strain-specific* - G1P[8] - G2P[4] - G3P[8] - G12P[8] *Age-specific* - 1st year of life - 2nd year of life - 3rd year of life - 4th year of life - 5th year of life - 6th-7th year of life	80% [74,84] 89% [55,97] 87% [65,95] 80% [64,89] 78% [71,84] 91% [78,96] 82% [69,89] 88% [78,93] 76% [51,88] 60% [16,81] 69% [43,84]	2011-2012 2012-2013

*Wang FT, et al. Effectiveness of the pentavalent rotavirus vaccine in preventing gastroenteritis in the United States. *Pediatrics.*125 (e208). 2009-1246. 2010.

†RVGE = Rotavirus Gastroenteritis

‡Gagneur, A, et al. Impact of rotavirus vaccination on hospitalizations for rotavirus diarrhea: The IVANHOE study. *Vaccine.* (29). 3753-3759. 2011.
§Payne DC, et al. Long-term consistency in rotavirus vaccine protection: RV5 and RV1 vaccine effectiveness in US children, 2012-2013. *Clin Infect Dis.*1-7. 2015.
¶RV-negative acute gastroenteritis controls

Safety, Efficacy, and Immunogenicity with Concomitant Administration of RotaTeq and Other Vaccines

RotaTeq was well tolerated and efficacious when administered concomitantly with other licensed childhood vaccines. The efficacy of RotaTeq was evaluated among a subset of infants in the US who received *Haemophilus influenzae* type b and hepatitis B vaccine, diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine, inactivated poliovirus vaccine (IPV), and pneumococcal conjugate vaccine. The efficacy of RotaTeq was 89.5% against rotavirus gastroenteritis of any severity caused by the composite of the G-serotypes included in the vaccine for the first rotavirus season after vaccination (see Table 8). The immune responses to the specified vaccines were largely unaffected by RotaTeq. Of the 17 antigens studied, the antibody responses were similar among vaccine and placebo recipients except for a slightly diminished response to one of the three antigens tested for pertussis (pertactin).

Table 8

Efficacy of RotaTeq against any severity of rotavirus gastroenteritis caused by the G-serotypes included in the vaccine in infants who received RotaTeq concomitantly with other licensed pediatric vaccines

	RotaTeq	Placebo	% Efficacy
Number of cases / Number of evaluable subjects			
Rotavirus Gastroenteritis Cases	1/602	10/637	89.5

Immunogenicity

A relationship between antibody responses to RotaTeq and protection against rotavirus gastroenteritis has not yet been established. However, RotaTeq induces antibodies that neutralize human serotypes G1, G2, G3, G4 and P1[8]. In phase III clinical studies, 92.9% to 100% of recipients of RotaTeq achieved a significant rise in serum anti-rotavirus IgA after a three-dose regimen.

IV. INDICATIONS

RotaTeq is an oral pentavalent vaccine indicated for the prevention of rotavirus gastroenteritis in infants and children caused by the serotypes G1, G2, G3, G4, and G-serotypes that contain P1A[8] (e.g., G9). RotaTeq may be administered as early as six weeks of age.

V. DOSAGE AND ADMINISTRATION

FOR ORAL USE ONLY. NOT FOR INJECTION.

Posology

The vaccination series consists of three ready-to-use liquid doses of RotaTeq administered orally to infants.

The first dose of RotaTeq should be administered at 6 to 12 weeks of age; the subsequent doses should be administered at a minimum interval of 4 weeks between each dose.

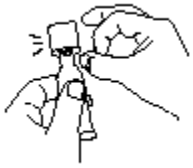
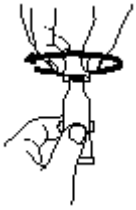
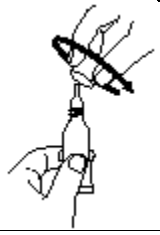
There are no restrictions on the infant's consumption of food or liquid, including breast milk, either before or after vaccination with RotaTeq.

RotaTeq may be given to pre-term infants according to their chronological age.

If for any reason an incomplete dose is administered (e.g., infant spits or regurgitates the vaccine), a replacement dose is not recommended, since such dosing was not studied in the clinical trials. The infant should continue to receive any remaining doses in the recommended series.

The vaccine is to be administered orally without mixing with any other vaccines or solutions. Do not reconstitute or dilute.

Each dose is supplied in a container consisting of a squeezable plastic, latex-free dosing tube with a twist-off cap, allowing for direct oral administration. The dosing tube is contained in a pouch.

To administer the vaccine:	
	Tear open the pouch and remove the dosing tube.
	Clear the fluid from the dispensing tip by holding tube vertically and tapping cap.
	Open the dosing tube in 2 easy motions: 1. Puncture the dispensing tip by screwing cap ***clockwise*** until it becomes tight.
	2. Remove cap by turning it ***counterclockwise***.
	Administer dose by gently squeezing liquid into infant's mouth toward the inner cheek until dosing tube is empty. (A residual drop may remain in the tip of the tube.)

	Discard the empty tube and cap in approved biological waste containers according to local regulations.

Use with Other Vaccines

RotaTeq can be administered with diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine, inactivated or oral poliovirus vaccine (IPV or OPV), *Haemophilus influenzae* type b conjugate vaccine, hepatitis B vaccine, pneumococcal conjugate vaccine, and hexavalent vaccines.

Concomitant administration of RotaTeq and oral poliovirus vaccine (OPV) does not affect the immune response to the poliovirus antigens. Although concomitant administration of OPV may slightly reduce the immune response to rotavirus vaccine, there is currently no evidence that clinical protection against severe rotavirus gastroenteritis would be affected. The immune response to RotaTeq is unaffected when OPV is administered two weeks after RotaTeq.

VI. CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine

Individuals who develop symptoms suggestive of hypersensitivity after receiving a dose of RotaTeq should not receive further doses of RotaTeq.

Individuals with Severe Combined Immunodeficiency Disease (SCID). Cases of gastroenteritis associated with vaccine virus have been reported post-marketing in infants with SCID.

VII. PRECAUTIONS

Adequate treatment provisions, including epinephrine injection (1:1000), should be available for immediate use should an anaphylactic reaction occur.

No safety or efficacy data are available from clinical trials regarding the administration of RotaTeq to:

1. immunocompromised patients such as
   - individuals with malignancies or who are otherwise immunocompromised;
   - individuals receiving immunosuppressive therapy;
2. individuals infected with HIV; or
3. individuals who have received a blood transfusion or blood products, including immunoglobulins within 42 days.

No fecal shedding of vaccine strains was seen in a small subset of infants with serious medical conditions (e.g., cystic fibrosis, failure to thrive, cancer, congenital heart disease, and neutropenia) that were diagnosed after enrollment in the study. Health care providers may want to consider these data when assessing the benefits and potential risks of administering RotaTeq to infants with serious medical conditions while keeping in mind nearly all children are infected with naturally occurring rotavirus by age 5 years.

In clinical trials, RotaTeq was not administered to infants known to have immunodeficient household members. In these trials, RotaTeq was shed in the stools of 8.9% of vaccine recipients almost exclusively in the week after dose 1 and in only one vaccine recipient (0.3%) after dose 3. Transmission of vaccine virus strains to non-vaccinated contacts has been observed post-marketing. RotaTeq should be administered with caution to individuals with immunodeficient close contacts such as:

- individuals with malignancies or who are otherwise immunocompromised; or
- individuals receiving immunosuppressive therapy.

However, because nearly all children are infected with naturally occurring rotavirus by the age of 5 years, vaccination of infants may decrease the risk of exposure of immunodeficient household contacts to naturally occurring rotavirus. The health care provider should assess the potential risks and benefits of administering RotaTeq to infants known to have immunodeficient close contacts.

Infants with active gastrointestinal illness, chronic diarrhea or growth retardation, or a history of congenital abdominal disorders or intussusception were not to be included in

the clinical studies. Administration of RotaTeq may be considered with caution in such infants when, in the opinion of the physician, withholding the vaccine entails a greater risk.

In worldwide post-marketing surveillance, cases of intussusception have been reported in temporal association with RotaTeq. (See XII. SIDE EFFECTS, *Post-marketing Reports*.)

Any acute infection or febrile illness may be reason for delaying use of RotaTeq except when, in the opinion of the physician, withholding the vaccine entails a greater risk. Low-grade fever itself and mild upper respiratory infection are not contraindications to vaccination with RotaTeq.

As with any vaccine, vaccination with RotaTeq may not result in complete protection in all recipients.

The clinical studies were not designed to assess the level of protection provided by only 1 or 2 doses of RotaTeq. Post hoc analyses of data from a large clinical study suggest that RotaTeq provides protection against hospitalizations and emergency department visits for rotavirus gastroenteritis during administration of the 3-dose vaccination series starting from 14 days post dose 1.

No clinical data are available for RotaTeq when administered after exposure to rotavirus.

VIII. PREGNANCY

RotaTeq is a pediatric vaccine and is not indicated for use in adults. There have been no adequate, well-controlled studies in women or animals.

IX. NURSING MOTHERS

As RotaTeq is a pediatric vaccine and is not indicated for use in adults, information on the safety of the vaccine when used during lactation is not available.

X. PEDIATRIC USE

RotaTeq has been shown to be generally well tolerated and highly efficacious in preventing rotavirus gastroenteritis when administered to infants 6 weeks through 32 weeks of age. (See V. DOSAGE AND ADMINISTRATION for the recommended dosage schedule.)

Safety and efficacy have not been established in infants less than 6 weeks of age.

XI. DRUG INTERACTIONS

There are no known drug interactions. (See V. DOSAGE AND ADMINISTRATION, *Use With Other Vaccines*.)

XII. SIDE EFFECTS

71,725 infants were evaluated in 3 placebo-controlled clinical trials including 36,165 infants who received RotaTeq and 35,560 infants who received placebo. Parents/guardians were contacted on days 7, 14, and 42 after each dose regarding intussusception and any other serious adverse events.

The vaccine is generally well tolerated.

In the large-scale (34,837 vaccine recipients and 34,788 placebo recipients), placebo-controlled Rotavirus Efficacy and Safety Trial (REST), RotaTeq did not increase the risk of intussusception relative to placebo (see Table 9). Active surveillance was employed to identify potential cases of intussusception at days 7, 14, and 42 after each dose and every 6 weeks thereafter for 1 year after dose one. There were no confirmed cases of intussusception during the 42-day period after dose one, and there was no clustering of cases among vaccine recipients at any time period after any dose. Following the 1-year safety follow-up period, 4 cases of intussusception were reported in children who had received placebo during the study.

Table 9

Confirmed Cases of Intussusception in Recipients of RotaTeq as Compared with Placebo Recipients during REST

	RotaTeq (n=34,837)	Placebo (n=34,788)
Confirmed intussusception cases within 42 days after each dose	6	5
Relative Risk (95% CI) †	1.6 (0.4, 6.4)	--
Confirmed intussusception cases within 365 days after dose one	13	15
Relative Risk (95% CI)	0.9 (0.4, 1.9)	--

† Relative Risk and 95% Confidence Interval based upon group sequential design stopping criteria employed in REST

Kawasaki's disease was reported in the phase III clinical trials in <0.1% (5/36,150) of vaccine recipients and <0.1% (1/35,536) of placebo recipients within 42 days of any dose (not statistically significant).

In 11,711 infants (6,138 recipients of RotaTeq) from the 3 studies, a Vaccination Report Card was used by parents/guardians to record the child’s temperature and any episodes of diarrhea and vomiting on a daily basis during the first week following each vaccination. Table 10 summarizes the frequencies of these adverse events, regardless of cause.

Table 10

Adverse Experiences of Special Clinical Interest within the First Week after the First Dose

Adverse Event	First Dose	
	RotaTeq	Placebo

Elevated Temperature (≥ 100.5°F [38.1°C] rectal equivalent)	17.1%	16.2%
Vomiting	6.7%	5.4%
Diarrhea	10.4%	9.1%

Parents/guardians of the 11,711 infants were also asked to report the presence of other events on the Vaccination Report Card for 42 days after each dose. The following vaccine-related adverse experiences were observed among recipients of RotaTeq at a frequency at least 0.3% greater than that observed among placebo recipients.

Very Common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1,000, <1/100); Rare (≥1/10,000, <1/1,000); Very Rare (<1/10,000)

Infections and infestations

Uncommon: nasopharyngitis (0.6% vaccine recipients, 0.3% placebo recipients)

Gastrointestinal disorders

Very Common: diarrhea (17.6% vaccine recipients, 15.1% placebo recipients), vomiting (10.1% vaccine recipients, 8.2% placebo recipients)

General disorders and administration site conditions

Very Common: pyrexia (20.9% vaccine recipients, 18.7% placebo recipients)

Other Adverse Events

Otitis media and bronchospasm occurred in more vaccine than placebo recipients (14.5% versus 13.0% and 1.1% versus 0.7%, respectively) overall; however, among cases that were considered to be vaccine-related in the opinion of the study investigator, the incidence was the same for vaccine and placebo recipients for otitis media (0.3%) and bronchospasm (<0.1%).

Administration of other licensed vaccines was permitted in all studies. The safety of RotaTeq when administered concomitantly with pre-specified licensed vaccines including *Haemophilus influenzae* type b and hepatitis B vaccine, diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine, inactivated poliovirus vaccine (IPV), pneumococcal conjugate vaccine, and hexavalent vaccines was evaluated in all 3 phase III, placebo-controlled studies. In a subsequent controlled study, the safety of RotaTeq when administered concomitantly with oral poliovirus vaccine was evaluated. RotaTeq was well tolerated; the frequency of adverse experiences observed was generally similar to that seen in the control group.

Post-marketing Reports

The following adverse experiences have been spontaneously reported during post-approval use of RotaTeq. Because these experiences were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish a causal relationship to vaccine exposure.

Immune system disorders: anaphylactic reaction.

Skin and subcutaneous tissue disorders: urticaria, angioedema.

Gastrointestinal disorders: gastroenteritis associated with vaccine viral shedding, intussusception.

Post-Marketing Observational Safety Surveillance Study

In a prospective post-marketing observational study conducted using a large medical claims database, the risks of intussusception or Kawasaki disease resulting in emergency department visits or hospitalizations during the 30 days following any dose of vaccine were analyzed among 85,150 infants receiving one or more doses of RotaTeq. Medical charts were reviewed to confirm these diagnoses. In addition, general safety was monitored by electronic search of the automated records database for all emergency department visits

and hospitalizations. The study included an independent, external Safety Monitoring Committee.

During the 0-30 day follow-up period after vaccination, there were no statistically significant differences in the rates of intussusception or Kawasaki disease compared with the expected background rates. In addition, there was no statistically significant increased risk of these adverse events during the 0-30 day follow-up period when comparing the 17,433 person-years of follow-up among infants receiving RotaTeq (n=85,150) with the 12,339 person-years of follow-up among a concurrent control group of infants who received DTaP, but not RotaTeq (n=62,617). There were 6 confirmed cases of intussusception among infants vaccinated with RotaTeq compared with 5 among the concurrent controls vaccinated with DTaP (relative risk = 0.8, 95% CI: 0.22-3.52). There was one chart-confirmed case of Kawasaki disease identified among infants vaccinated with RotaTeq and one chart-confirmed case of Kawasaki disease among concurrent DTaP controls (relative risk = 0.7, 95% CI: 0.01-55.56). In the general safety analyses, the Safety Monitoring Committee did not identify any specific safety concerns. (See VII. PRECAUTIONS.)

XIII. OVERDOSAGE

There have been reports of administration of higher than recommended doses of RotaTeq. In general, the adverse event profile reported with overdose was comparable to that observed with recommended doses of RotaTeq.

XIV. APPEARANCE & AVAILABILITY

Appearance: pale yellow to pale yellow with a pink tint; clear liquid.

RotaTeq is available as a single or ten packs of pre-filled 2 mL unit dose in a plastic dosing tube with a twist-off cap. The dosing tube is contained in a pouch. The container and delivery system are latex-free.

XV. STORAGE

Store and transport refrigerated at 2°C to 8°C.
Protect from light.
The product must be used before the expiration date.

RotaTeq should be administered as soon as possible after being removed from refrigeration. When out of refrigeration at room temperature at or below 25°C, administration may be delayed for up to 48 hours. After this time, the vaccine should be discarded in approved biological waste containers according to local regulations.

XVI. SHELF LIFE

Please refer to the expiry date on the outer carton.

XVII. MANUFACTURER & PACKER

Merck Sharp & Dohme LLC
770, Sumneytown Pike,
West Point, PA 19486, U.S.A.

XVIII. PRODUCT REGISTRATION HOLDER

MERCK SHARP & DOHME (MALAYSIA) SDN. BHD.
Lot No. B-22-1 & B-22-2, Level 22
The Ascent, Paradigm No. 1
Jalan SS 7/26A, Kelana Jaya
47301 Petaling Jaya
Selangor, Malaysia.

Date of revision: 19 Aug 2025