

1 NAME OF THE MEDICINAL PRODUCT

RotaTeq[®] (Rotavirus Vaccine, Live, Oral, Pentavalent)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose contains:

Rotavirus G1 Reassortant	not less than 2.2×10^6 IU ¹
Rotavirus G2 Reassortant	not less than 2.8×10^6 IU ¹
Rotavirus G3 Reassortant	not less than 2.2×10^6 IU ¹
Rotavirus G4 Reassortant	not less than 2.0×10^6 IU ¹
Rotavirus P1A[8] Reassortant	not less than 2.3×10^6 IU ¹

¹ Infectious Units

Excipients with known effect

This vaccine contains 1080 milligrams sucrose and 37.6 milligrams sodium (see section 8.10 and 8.11).

For the full list of excipients, see section 13.

3 PHARMACEUTICAL FORM

Oral Solution

4 THERAPEUTIC INDICATIONS

RotaTeq[®] is indicated for the prevention of rotavirus gastroenteritis in infants and children caused by types G1, G2, G3, G4, and G9 when administered as a 3-dose series to infants between the ages of 6 to 32 weeks. The first dose of RotaTeq should be administered between 6 and 12 weeks of age. [see *Dosage and Administration* (5)].

5 DOSAGE AND ADMINISTRATION

FOR ORAL USE ONLY. NOT FOR INJECTION.

The vaccination series consists of three ready-to-use liquid doses of RotaTeq administered orally starting at 6 to 12 weeks of age, with the subsequent doses administered at 4 to 10 week intervals. The third dose should not be given after 32 weeks of age [see *Clinical Studies* (16)].

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

Do not mix the RotaTeq vaccine with any other vaccines or solutions. Do not reconstitute or dilute [see *Dosage and Administration* (5.2)].

For storage instructions [see *How Supplied/Storage and Handling* (17.1)].

Each dose is supplied in a container consisting of a squeezable plastic tube with a twist-off cap, allowing for direct oral administration. The tube is contained in a pouch [see *Dosage and Administration* (5.2)].

5.1 Use with Other Vaccines

In clinical trials, RotaTeq was administered concomitantly with other licensed pediatric vaccines [see *Adverse Reactions* (9.1), *Drug Interactions* (10.1), and *Clinical Studies* (16)].

5.2 Instructions for Use

To administer the vaccine:



Step 1: Tear open the pouch and remove the tube.



Step 2: Clear the fluid from the dispensing tip by holding tube vertically and tapping cap.

Open the tube in 2 easy motions as shown in figures accompanying Steps 3 and 4:



Step 3:

1. Puncture the dispensing tip by screwing cap **clockwise** until it becomes tight.



Step 4:

2. Remove cap by turning it **counterclockwise**.



Step 5: Administer dose by gently squeezing liquid into infant's mouth toward the inner cheek until tube is empty. (A residual drop may remain in the tip of the tube.)

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.

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

6 DOSAGE FORMS AND STRENGTHS

Oral solution. Each dose is 2 mL.

7 CONTRAINDICATIONS

7.1 Hypersensitivity

RotaTeq is contraindicated in infants with hypersensitivity to the active substance or to any of the excipients listed in section 13. Infants who develop symptoms suggestive of hypersensitivity after receiving a dose of RotaTeq should not receive further doses of RotaTeq.

7.2 Severe Combined Immunodeficiency Disease

RotaTeq is contraindicated in infants with Severe Combined Immunodeficiency Disease (SCID) and should not receive RotaTeq. Postmarketing reports of gastroenteritis, including severe diarrhea and prolonged shedding of vaccine virus, have been reported in infants who were administered RotaTeq and later identified as having SCID.

7.3 History of Intussusception

RotaTeq is contraindicated in infants with a history of intussusception and should not receive RotaTeq.

8 WARNINGS AND PRECAUTIONS

8.1 Managing Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

8.2 Immunocompromised Populations

No safety or efficacy data are available from clinical trials regarding the administration of RotaTeq to infants who are potentially immunocompromised including:

- Infants with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic system.
- Infants on immunosuppressive therapy (including high-dose systemic corticosteroids). RotaTeq may be administered to infants who are being treated with topical corticosteroids or inhaled steroids.
- Infants with primary and acquired immunodeficiency states, including HIV/AIDS or other clinical manifestations of infection with human immunodeficiency viruses; cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states. There are insufficient data from the clinical trials to support administration of RotaTeq to infants with indeterminate HIV status who are born to mothers with HIV/AIDS.
- Infants who have received a blood transfusion or blood products, including immunoglobulins within 42 days.
- Immunosuppressive therapies including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to RotaTeq.

Vaccine virus transmission from vaccine recipient to non-vaccinated contacts has been reported [see *Warnings and Precautions (8.5)*].

8.3 Intussusception

Following administration of a previously licensed live rhesus rotavirus reassortant vaccine, an increased risk of intussusception was observed.

In a postmarketing observational study in the US cases of intussusception were observed in temporal association within 21 days following the first dose of RotaTeq, with a clustering of cases in the first 7 days. [see *Adverse Reactions (9.2)*].

In worldwide passive postmarketing surveillance, cases of intussusception have been reported in temporal association with RotaTeq. [see *Adverse Reactions (9.2)*].

8.4 Gastrointestinal Illness

No safety or efficacy data are available for administration of RotaTeq to infants with a history of gastrointestinal disorders including infants with active acute gastrointestinal illness, infants with chronic diarrhea and failure to thrive, and infants with a history of congenital abdominal disorders, and abdominal surgery. Caution is advised when considering administration of RotaTeq to these infants.

8.5 Shedding and Transmission

Shedding of vaccine virus was evaluated among a subset of subjects in the Rotavirus Efficacy and Safety Trial (Study 006, also known as REST) 4 to 6 days after each dose and among all subjects who

submitted a stool antigen rotavirus positive sample at any time. RotaTeq was shed in the stools of 32 of 360 [8.9%, 95% CI (6.2%, 12.3%)] vaccine recipients tested after dose 1; 0 of 249 [0.0%, 95% CI (0.0%, 1.5%)] vaccine recipients tested after dose 2; and in 1 of 385 [0.3%, 95% CI (<0.1%, 1.4%)] vaccine recipients after dose 3. In phase 3 studies, shedding was observed as early as 1 day and as late as 15 days after a dose. Transmission of vaccine virus was not evaluated in phase 3 studies.

Transmission of vaccine virus strains from vaccinees to non-vaccinated contacts has been observed postmarketing.

The potential risk of transmission of vaccine virus should be weighed against the risk of acquiring and transmitting natural rotavirus.

Caution is advised when considering whether to administer RotaTeq to individuals with immunodeficient close contacts such as:

- Individuals with malignancies or who are otherwise immunocompromised;
- Individuals with primary immunodeficiency; or
- Individuals receiving immunosuppressive therapy.

8.6 Febrile Illness

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 (<100.5°F [38.1°C]) itself and mild upper respiratory infection do not preclude vaccination with RotaTeq.

8.7 Incomplete Regimen

The clinical studies were not designed to assess the level of protection provided by only one or two doses of RotaTeq.

8.8 Limitations of Vaccine Effectiveness

RotaTeq may not protect all vaccine recipients against rotavirus.

8.9 Post-Exposure Prophylaxis

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

8.10 Sucrose
RotaTeq contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this vaccine. See section 2.

8.11 Sodium

This vaccine contains 37.6 mg sodium per dose, equivalent to 1.88% of the WHO recommended maximum daily intake of 2 g sodium for an adult. See section 2.

9 ADVERSE REACTIONS

9.1 Clinical Studies Experience

71,725 infants were evaluated in 3 placebo-controlled clinical trials including 36,165 infants in the group that received RotaTeq and 35,560 infants in the group that received placebo. Parents/guardians were contacted on days 7, 14, and 42 after each dose regarding intussusception and any other serious adverse events. The racial distribution was as follows: White (69% in both groups); Hispanic-American (14% in both groups); Black (8% in both groups); Multiracial (5% in both groups); Asian (2% in both groups); Native American (RotaTeq 2%, placebo 1%); and Other (<1% in both groups). The gender distribution was 51% male and 49% female in both vaccination groups.

Because clinical trials are conducted under conditions that may not be typical of those observed in clinical practice, the adverse reaction rates presented below may not be reflective of those observed in clinical practice.

Serious Adverse Events

Serious adverse events occurred in 2.4% of recipients of RotaTeq when compared to 2.6% of placebo recipients within the 42-day period of a dose in the phase 3 clinical studies of RotaTeq. The most frequently reported serious adverse events for RotaTeq compared to placebo were:

bronchiolitis	(0.6% RotaTeq vs. 0.7% Placebo),
gastroenteritis	(0.2% RotaTeq vs. 0.3% Placebo),
pneumonia	(0.2% RotaTeq vs. 0.2% Placebo),

fever (0.1% RotaTeq vs. 0.1% Placebo), and
urinary tract infection (0.1% RotaTeq vs. 0.1% Placebo).

Deaths

Across the clinical studies, 52 deaths were reported. There were 25 deaths in the RotaTeq recipients compared to 27 deaths in the placebo recipients. The most commonly reported cause of death was sudden infant death syndrome, which was observed in 8 recipients of RotaTeq and 9 placebo recipients.

Intussusception

In Study 006, 34,837 vaccine recipients and 34,788 placebo recipients were monitored by active surveillance to identify potential cases of intussusception at 7, 14, and 42 days after each dose, and every 6 weeks thereafter for 1 year after the first dose.

For the primary safety outcome, cases of intussusception occurring within 42 days of any dose, there were 6 cases among RotaTeq recipients and 5 cases among placebo recipients (see Table 1). The data did not suggest an increased risk of intussusception relative to placebo.

Table 1: Confirmed cases of intussusception in recipients of RotaTeq as compared with placebo recipients during Study 006

	RotaTeq (n=34,837)	Placebo (n=34,788)
Confirmed intussusception cases within 42 days of any dose	6	5
Relative risk (95% CI) [*]	1.6 (0.4, 6.4)	
Confirmed intussusception cases within 365 days of dose 1	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 Study 006.

Among vaccine recipients, there were no confirmed cases of intussusception within the 42 day period after the first dose, which was the period of highest risk for the rhesus rotavirus-based product (see Table 2).

Table 2: Intussusception cases by day range in relation to dose in Study 006

Day Range	Dose 1		Dose 2		Dose 3		Any Dose	
	RotaTeq	Placebo	RotaTeq	Placebo	RotaTeq	Placebo	RotaTeq	Placebo
1-7	0	0	1	0	0	0	1	0
1-14	0	0	1	0	0	1	1	1
1-21	0	0	3	0	0	1	3	1
1-42	0	1	4	1	2	3	6	5

All of the children who developed intussusception recovered without sequelae with the exception of a 9-month-old male who developed intussusception 98 days after dose 3 and died of post-operative sepsis. There was a single case of intussusception among 2,470 recipients of RotaTeq in a 7-month-old male in the phase 1 and 2 studies (716 placebo recipients).

Hematochezia

Hematochezia reported as an adverse experience occurred in 0.6% (39/6,130) of vaccine and 0.6% (34/5,560) of placebo recipients within 42 days of any dose. Hematochezia reported as a serious adverse experience occurred in <0.1% (4/36,150) of vaccine and <0.1% (7/35,536) of placebo recipients within 42 days of any dose.

Seizures

All seizures reported in the phase 3 trials of RotaTeq (by vaccination group and interval after dose) are shown in Table 3.

Table 3: Seizures reported by day range in relation to any dose in the phase 3 trials of RotaTeq

Day range	1-7	1-14	1-42
RotaTeq	10	15	33
Placebo	5	8	24

Seizures reported as serious adverse experiences occurred in <0.1% (27/36,150) of vaccine and <0.1% (18/35,536) of placebo recipients (not significant). Ten febrile seizures were reported as serious adverse experiences, 5 were observed in vaccine recipients and 5 in placebo recipients.

Kawasaki Disease

In the phase 3 clinical trials, infants were followed for up to 42 days of vaccine dose. Kawasaki disease was reported in 5 of 36,150 vaccine recipients and in 1 of 35,536 placebo recipients with unadjusted relative risk 4.9 (95% CI 0.6, 239.1).

Most Common Adverse Events

Solicited Adverse Events

Detailed safety information was collected from 11,711 infants (6,138 recipients of RotaTeq) which included a subset of subjects in Study 006 and all subjects from Studies 007 and 009 (Detailed Safety Cohort). 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 4 summarizes the frequencies of these adverse events and irritability.

Table 4: Solicited adverse experiences within the first week after doses 1, 2, and 3 (Detailed Safety Cohort)

Adverse experience	Dose 1		Dose 2		Dose 3	
	RotaTeq	Placebo	RotaTeq	Placebo	RotaTeq	Placebo
Elevated temperature*	n=5,616 17.1%	n=5,077 16.2%	n=5,215 20.0%	n=4,725 19.4%	n=4,865 18.2%	n=4,382 17.6%
Vomiting	n=6,130 6.7%	n=5,560 5.4%	n=5,703 5.0%	n=5,173 4.4%	n=5,496 3.6%	n=4,989 3.2%
Diarrhea	10.4%	9.1%	8.6%	6.4%	6.1%	5.4%
Irritability	7.1%	7.1%	6.0%	6.5%	4.3%	4.5%

* Temperature $\geq 100.5^{\circ}\text{F}$ [38.1°C] rectal equivalent obtained by adding 1 degree F to otic and oral temperatures and 2 degrees F to axillary temperatures

Other Adverse Events

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.

Fever was observed at similar rates in vaccine (N=6,138) and placebo (N=5,573) recipients (42.6% vs. 42.8%). Adverse events that occurred at a statistically higher incidence (i.e., 2-sided p-value <0.05) within the 42 days of any dose among recipients of RotaTeq as compared with placebo recipients are shown in Table 5.

Table 5: Adverse events that occurred at a statistically higher incidence within 42 days of any dose among recipients of RotaTeq as compared with placebo recipients

Adverse event	RotaTeq N=6,138	Placebo N=5,573
	n (%)	n (%)
Diarrhea	1,479 (24.1%)	1,186 (21.3%)
Vomiting	929 (15.2%)	758 (13.6%)
Otitis media	887 (14.5%)	724 (13.0%)
Nasopharyngitis	422 (6.9%)	325 (5.8%)
Bronchospasm	66 (1.1%)	40 (0.7%)

Safety in Pre-Term Infants

RotaTeq or placebo was administered to 2,070 pre-term infants (25 to 36 weeks gestational age, median 34 weeks) according to their age in weeks since birth in Study 006. All pre-term infants were followed for serious adverse experiences; a subset of 308 infants was monitored for all adverse experiences. There were 4 deaths throughout the study, 2 among vaccine recipients (1 SIDS and 1 motor vehicle accident) and 2 among placebo recipients (1 SIDS and 1 unknown cause). No cases of intussusception were reported. Serious adverse experiences occurred in 5.5% of vaccine and 5.8% of placebo recipients. The most common serious adverse experience was bronchiolitis, which occurred in 1.4% of vaccine and 2.0% of placebo recipients. Parents/guardians were asked to record the child's temperature and any episodes of vomiting and diarrhea daily for the first week following vaccination. The frequencies of these adverse experiences and irritability within the week after dose 1 are summarized in Table 6.

Table 6
Solicited adverse experiences within the first week of doses 1, 2, and 3 among pre-term infants

Adverse event	Dose 1		Dose 2		Dose 3	
	RotaTeq	Placebo	RotaTeq	Placebo	RotaTeq	Placebo
	N=127	N=133	N=124	N=121	N=115	N=108
Elevated temperature*	18.1%	17.3%	25.0%	28.1%	14.8%	20.4%
	N=154	N=154	N=137	N=137	N=135	N=129
Vomiting	5.8%	7.8%	2.9%	2.2%	4.4%	4.7%
Diarrhea	6.5%	5.8%	7.3%	7.3%	3.7%	3.9%
Irritability	3.9%	5.2%	2.9%	4.4%	8.1%	5.4%

*Temperature $\geq 100.5^{\circ}\text{F}$ [38.1°C] rectal equivalent obtained by adding 1 degree F to otic and oral temperatures and 2 degrees F to axillary temperatures

9.2 Postmarketing Experience

The following adverse events have been identified during post-approval use of RotaTeq from reports to the Vaccine Adverse Event Reporting System (VAERS).

Reporting of adverse events following immunization to VAERS is voluntary, and the number of doses of vaccine administered is not known; therefore, it is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to vaccine exposure using VAERS data.

In postmarketing experience, the following adverse events have been reported following the use of RotaTeq:

Immune system disorders:

Anaphylactic reaction

Gastrointestinal disorders:

Intussusception (including death)

Hematochezia

Gastroenteritis associated with prolonged vaccine viral shedding in infants with Severe Combined Immunodeficiency Disease (SCID) resulting in severe diarrhea [see *Contraindications* (7.2)].

Acute gastroenteritis associated with vaccine viral shedding in infants without known immune deficiency

Skin and subcutaneous tissue disorders:

Urticaria

Angioedema

Infections and infestations

Kawasaki disease

Transmission of vaccine virus strains from vaccine recipient to non-vaccinated contacts.

Postmarketing Observational Safety Surveillance Studies

The temporal association between vaccination with RotaTeq and intussusception was evaluated in the Post-licensure Rapid Immunization Safety Monitoring (PRISM) program², an electronic active surveillance program comprised of 3 US health insurance plans.

More than 1.2 million RotaTeq vaccinations (507,000 of which were first doses) administered to infants 5 through 36 weeks of age were evaluated. From 2004 through 2011, potential cases of intussusception in either the inpatient or emergency department setting and vaccine exposures were identified through electronic procedure and diagnosis codes. Medical records were reviewed to confirm intussusception and rotavirus vaccination status.

The risk of intussusception was assessed using self-controlled risk interval and cohort designs, with adjustment for age. Risk windows of 1-7 and 1-21 days were evaluated. Cases of intussusception were observed in temporal association within 21 days following the first dose of RotaTeq, with a clustering of cases in the first 7 days. Based on the results, approximately 1 to 1.5 excess cases of intussusception occur per 100,000 vaccinated US infants within 21 days following the first dose of RotaTeq. In the first year of life, the background rate of intussusception hospitalizations in the US has been estimated to be approximately 34 per 100,000 infants.³

In an earlier prospective postmarketing observational cohort study conducted using a large US 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 from February 2006 through March 2009. Medical charts were reviewed to confirm these diagnoses. Evaluation included concurrent (n = 62,617) and historical (n=100,000 from 2001-2005) control groups of infants who received diphtheria, tetanus and acellular pertussis vaccine (DTaP) but not RotaTeq.

Confirmed intussusception cases in the RotaTeq group were compared with those in the concurrent DTaP control group and in the historical control group. The data were analyzed post-dose 1 and post any dose, in both 7 day and 30 day risk windows. A statistically significant increased risk of intussusception after RotaTeq vaccination was not observed.

One confirmed case of Kawasaki disease (23 days post-dose 3) was identified among infants vaccinated with RotaTeq and one confirmed case of Kawasaki disease (22 days post-dose 2) was identified among concurrent DTaP controls (relative risk = 0.7; 95% CI: 0.01-55.56).

In addition, general safety was monitored by electronic search of the automated records database for all emergency department visits and hospitalizations in the 30 day period after each dose of RotaTeq compared with: 1) days 31-60 after each dose of RotaTeq (self-matched controls) and 2) the 30 day period after each dose of DTaP vaccine (historical control subset from 2004-2005, n=40,000). In safety analyses which evaluated multiple follow-up windows after vaccination (days: 0-7, 1-7, 8-14 and 0-30), no safety concerns were identified for infants vaccinated with RotaTeq when compared with self-matched controls and the historical control subset.

Reporting Adverse Events

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>

10 DRUG INTERACTIONS

10.1 Concomitant Vaccine Administration

In clinical trials, RotaTeq was administered concomitantly with diphtheria and tetanus toxoids and acellular pertussis (DTaP), inactivated poliovirus vaccine (IPV), H. influenzae type b conjugate (Hib), hepatitis B vaccine, and pneumococcal conjugate vaccine [see *Adverse Reactions (9.1), Clinical Studies (16)*].

There was no evidence for reduced antibody responses to the vaccines that were concomitantly administered with RotaTeq.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

RotaTeq is not approved for individuals 32 weeks of age and older. No human or animal data are available to assess vaccine-associated risks in pregnancy.

11.2 Lactation

No human or animal data are available to assess the impact of RotaTeq on milk production, its presence in breast milk, or its effect on the breastfed infant.

11.3 Pediatric Use

Safety and effectiveness of RotaTeq have not been established in infants less than 6 weeks of age or greater than 32 weeks of age.

Data are available from clinical studies to support the use of RotaTeq in pre-term infants according to their age in weeks since birth [see *Adverse Reactions (9.1)*].

Data are available from clinical studies to support the use of RotaTeq in infants with controlled gastroesophageal reflux disease.

12 OVERDOSAGE

There have been postmarketing reports of infants who received more than one dose or a replacement dose of RotaTeq after regurgitation [see *Dosage and Administration (5.2)*]. In limited postmarketing

experience of reported overdosage, the adverse events reported after incorrect administration of higher than recommended doses of RotaTeq were similar to adverse events observed with the approved dosage and schedule.

13 DESCRIPTION

RotaTeq is a live, oral pentavalent vaccine that contains 5 live reassortant rotaviruses. The rotavirus parent strains of the reassortants were isolated from human and bovine hosts. Four reassortant rotaviruses express one of the outer capsid proteins (G1, G2, G3, or G4) from the human rotavirus parent strain and the attachment protein (type P7) from the bovine rotavirus parent strain. The fifth reassortant virus expresses the attachment protein, P1A (genotype P[8]), herein referred to as type P1A[8], from the human rotavirus parent strain and the outer capsid protein of type G6 from the bovine rotavirus parent strain (see Table 7).

Table 7

Name of Reassortant	Human Rotavirus Parent Strains and Outer Surface Protein Compositions	Bovine Rotavirus Parent Strain and Outer Surface Protein Composition	Reassortant Outer Surface Protein Composition (Human Rotavirus Component in Bold)	Minimum Dose Levels (10 ⁶ infectious units)
G1	WI79 – G1P1A[8]	WC3 - G6, P7[5]	G1 P7[5]	2.2
G2	SC2 – G2P2[6]		G2 P7[5]	2.8
G3	WI78 – G3P1A[8]		G3 P7[5]	2.2
G4	BrB – G4P2[6]		G4 P7[5]	2.0
P1A[8]	WI79 – G1P1A[8]		G6 P1A [8]	2.3

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

The reassortants are suspended in a buffered stabilizer solution. Each vaccine dose contains sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture media, and trace amounts of fetal bovine serum. RotaTeq contains no preservatives.

RotaTeq, an oral solution, is a pale yellow clear liquid that may have a pink tint.

RotaTeq is supplied in a plastic tube. The plastic tube and cap are not made with natural rubber latex.

14 CLINICAL PHARMACOLOGY

Rotavirus is a leading cause of severe acute gastroenteritis in infants and young children, with over 95% of these children infected by the time they are 5 years old. The most severe cases occur among infants and young children between 6 months and 24 months of age.

14.1 Mechanism of Action

The exact immunologic mechanism by which RotaTeq protects against rotavirus gastroenteritis is unknown [see *Clinical Studies* (16.6)]. RotaTeq is a live viral vaccine that replicates in the small intestine and induces immunity.

15 NONCLINICAL TOXICOLOGY

15.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

RotaTeq has not been evaluated for its carcinogenic or mutagenic potential or its potential to impair fertility.

16 CLINICAL STUDIES

Overall, 73,086 infants were randomized in 4 placebo-controlled, phase 3 studies conducted in 12 countries on 4 continents. The data demonstrating the efficacy of RotaTeq in preventing rotavirus gastroenteritis come from 7,744 of these infants from the US (including Navajo and White Mountain Apache Nations), Finland, and Japan who were enrolled in 3 of these studies: Study 006, Study 007, and Study 029. A fourth trial, Study 009, provided clinical evidence supporting the consistency of manufacture and contributed data to the overall safety evaluation.

The racial distribution of the efficacy subset was as follows: White (RotaTeq 61%, placebo 62%); Hispanic-American (RotaTeq 9%, placebo 8%); Black (2% in both groups); Multiracial (4% in both

groups); Asian (10% in both groups); Native American (13% in both groups); and Other (<1% in both groups). The gender distribution was 52% male and 48% female in both vaccination groups.

The efficacy evaluations in these studies included: 1) Prevention of any grade of severity of rotavirus gastroenteritis; 2) Prevention of severe rotavirus gastroenteritis, as defined by a clinical scoring system; and 3) Reduction in hospitalizations due to rotavirus gastroenteritis.

The vaccine was given as a three-dose series to healthy infants with the first dose administered between 6 and 12 weeks of age and followed by two additional doses administered at 4 to 10 week intervals. The age of infants receiving the third dose was 32 weeks of age or less. Oral polio vaccine administration was not permitted; however, other childhood vaccines could be concomitantly administered. Breast-feeding was permitted in all studies.

The case definition for rotavirus gastroenteritis used to determine vaccine efficacy required that a subject meet both of the following clinical and laboratory criteria: (1) greater than or equal to 3 watery or looser-than-normal stools within a 24-hour period and/or forceful vomiting; and (2) rotavirus antigen detection by enzyme immunoassay (EIA) in a stool specimen taken within 14 days of onset of symptoms. The severity of rotavirus acute gastroenteritis was determined by a clinical scoring system that took into account the intensity and duration of symptoms of fever, vomiting, diarrhea, and behavioral changes.

The primary efficacy analyses included cases of rotavirus gastroenteritis caused by types G1, G2, G3, G4 (and G types containing P1A8 (in Study 029 only)) that occurred at least 14 days after the third dose through the first rotavirus season post vaccination.

Analyses were also done to evaluate the efficacy of RotaTeq against rotavirus gastroenteritis caused by any of types G1, G2, G3, and G4 (and G types containing P1A8 (in Study 029 only)) at any time following the first dose through the first rotavirus season postvaccination among infants who received at least one vaccination (Intent-to-treat, ITT).

16.1 Rotavirus Efficacy and Safety Trial (Study 006)

Primary efficacy against any grade of severity of rotavirus gastroenteritis caused by naturally occurring types G1, G2, G3, or G4 through the first rotavirus season after vaccination was 74.0% (95% CI: 66.8, 79.9) and the ITT efficacy was 60.0% (95% CI: 51.5, 67.1). Primary efficacy against severe rotavirus gastroenteritis caused by naturally occurring types G1, G2, G3, or G4 through the first rotavirus season after vaccination was 98.0% (95% CI: 88.3, 100.0), and ITT efficacy was 96.4% (95% CI: 86.2, 99.6). See Table 8.

Table 8: Efficacy of RotaTeq against any grade of severity of and severe* G1-4 rotavirus gastroenteritis through the first rotavirus season postvaccination in Study 006

	Per Protocol		Intent-to-Treat [†]	
	RotaTeq	Placebo	RotaTeq	Placebo
Subjects vaccinated	2,834	2,839	2,834	2,839
Gastroenteritis cases				
Any grade of severity	82	315	150	371
Severe*	1	51	2	55
Efficacy estimate % and (95% confidence interval)				
Any grade of severity	74.0 (66.8, 79.9)		60.0 (51.5, 67.1)	
Severe*	98.0 (88.3, 100.0)		96.4 (86.2, 99.6)	

*Severe gastroenteritis defined by a clinical scoring system based on the intensity and duration of symptoms of fever, vomiting, diarrhea, and behavioral changes

[†]ITT analysis includes all subjects in the efficacy cohort who received at least one dose of vaccine.

The efficacy of RotaTeq against severe disease was also demonstrated by a reduction in hospitalizations for rotavirus gastroenteritis among all subjects enrolled in Study 006. RotaTeq reduced hospitalizations for rotavirus gastroenteritis caused by types G1, G2, G3, and G4 through the first two years after the third dose by 95.8% (95% CI: 90.5, 98.2). The ITT efficacy in reducing hospitalizations was 94.7% (95% CI: 89.3, 97.3) as shown in Table 9.

Table 9: Efficacy of RotaTeq in reducing G1-4 rotavirus-related hospitalizations in Study 006

	Per Protocol		Intent-to-Treat*	
	RotaTeq	Placebo	RotaTeq	Placebo
Subjects vaccinated	34,035	34,003	34,035	34,003
Number of hospitalizations	6	144	10	187
Efficacy estimate % and (95% confidence interval)	95.8 (90.5, 98.2)		94.7 (89.3, 97.3)	

*ITT analysis includes all subjects who received at least one dose of vaccine.

16.2 Study 007

Primary efficacy against any grade of severity of rotavirus gastroenteritis caused by naturally occurring types G1, G2, G3, or G4 through the first rotavirus season after vaccination was 72.5% (95% CI: 50.6, 85.6) and the ITT efficacy was 58.4% (95% CI: 33.8, 74.5). Primary efficacy against severe rotavirus gastroenteritis caused by naturally occurring types G1, G2, G3, or G4 through the first rotavirus season after vaccination was 100% (95% CI: 13.0, 100.0) and ITT efficacy against severe rotavirus disease was 100% (95% CI: 30.2, 100.0) as shown in Table 10.

Table 10:
Efficacy of RotaTeq against any grade of severity of and severe* G1-4 rotavirus gastroenteritis through the first rotavirus season postvaccination in Study 007

	Per Protocol		Intent-to-Treat†	
	RotaTeq	Placebo	RotaTeq	Placebo
Subjects vaccinated	650	660	650	660
Gastroenteritis cases				
Any grade of severity	15	54	27	64
Severe*	0	6	0	7
Efficacy estimate % and (95% confidence interval)				
Any grade of severity	72.5 (50.6, 85.6)		58.4 (33.8, 74.5)	
Severe*	100.0 (13.0, 100.0)		100.0 (30.2, 100.0)	

*Severe gastroenteritis defined by a clinical scoring system based on the intensity and duration of symptoms of fever, vomiting, diarrhea, and behavioral change

†ITT analysis includes all subjects in the efficacy cohort who received at least one dose of vaccine.

16.3 Multiple Rotavirus Seasons

The efficacy of RotaTeq through a second rotavirus season was evaluated in a single study (Study 006). Efficacy against any grade of severity of rotavirus gastroenteritis caused by rotavirus types G1, G2, G3, and G4 through the two rotavirus seasons after vaccination was 71.3% (95% CI: 64.7, 76.9). The efficacy of RotaTeq in preventing cases occurring only during the second rotavirus season postvaccination was 62.6% (95% CI: 44.3, 75.4). The efficacy of RotaTeq beyond the second season postvaccination was not evaluated.

16.4 Rotavirus Gastroenteritis Regardless of Type

The rotavirus types identified in the efficacy subset of Study 006 and Study 007 were G1P1A[8]; G2P1[4]; G3P1A[8]; G4P1A[8]; and G9P1A[8].

In Study 006, the efficacy of RotaTeq against any grade of severity of naturally occurring rotavirus gastroenteritis regardless of type was 71.8% (95% CI: 64.5, 77.8) and efficacy against severe rotavirus disease was 98.0% (95% CI: 88.3, 99.9). The ITT efficacy starting at dose 1 was 50.9% (95% CI: 41.6, 58.9) for any grade of severity of rotavirus disease and was 96.4% (95% CI: 86.3, 99.6) for severe rotavirus disease.

In Study 007, the primary efficacy of RotaTeq against any grade of severity of rotavirus gastroenteritis regardless of type was 72.7% (95% CI: 51.9, 85.4) and efficacy against severe rotavirus disease was 100% (95% CI: 12.7, 100). The ITT efficacy starting at dose 1 was 48.0% (95% CI: 21.6, 66.1) for any grade of severity of rotavirus disease and was 100% (95% CI: 30.4, 100.0) for severe rotavirus disease.

16.5 Rotavirus Gastroenteritis by Type

The efficacy against any grade of severity of rotavirus gastroenteritis by type was evaluated in Study 006 and Study 029. The efficacy cohort analysis from Study 006 is shown in Table 11.

Table 11: Type-specific efficacy of RotaTeq against any grade of severity of rotavirus gastroenteritis among infants in Study 006 efficacy cohort through the first rotavirus season postvaccination (Per Protocol)

Type identified by PCR	Number of cases		% Efficacy (95% Confidence Interval)
	RotaTeq (N=2,834)	Placebo (N=2,839)	
G1P1A[8]	72	286	74.9 (67.3, 80.9)
G2P1[4]	6	17	63.4 (2.6, 88.2)
G3P1A[8]	1	6	NS
G4P1A[8]	3	6	NS
G9P1A[8]	1	3	NS
Unidentified*	11	15	NS

N=number vaccinated

NS=not significant

*Includes rotavirus antigen-positive samples in which the specific type could not be identified by PCR

Additional analyses were conducted to evaluate efficacy in the prevention of rotavirus gastroenteritis due to G9P1A[8].

- In Study 029 (a Phase 3 randomized, blinded, placebo-controlled study conducted in Japan), efficacy on the pre-specified primary endpoint (rotavirus gastroenteritis caused by G1, G2, G3, G4, and G-serotypes associated with serotype P1A[8] (e.g., G9)) was 74.5% (95% CI: 39.9, 90.6). G9P1A[8]-associated gastroenteritis was observed in 0/356 and 5/354 subjects in the RotaTeq and placebo groups, respectively (100% (95% CI: -9.0, 100)).
- In a post hoc analysis of health care utilization data from 68,038 infants (RotaTeq 34,035 and placebo 34,003) in Study 006, using a case definition that included culture confirmation, hospitalization and emergency departments visits for rotavirus gastroenteritis cases due to G9P1A[8] were reduced (RotaTeq 0 cases: placebo 14 cases) by 100% (95% CI: 69.6, 100.0).

16.6 Immunogenicity

A relationship between antibody responses to RotaTeq and protection against rotavirus gastroenteritis has not been established. In phase 3 studies, 92.9% to 100% of 439 recipients of RotaTeq achieved a 3-fold or more rise in serum anti-rotavirus IgA after a three-dose regimen when compared to 12.3%-20.0% of 397 placebo recipients.

17 HOW SUPPLIED/STORAGE AND HANDLING

RotaTeq, 2 mL, a solution for oral use, is a pale yellow clear liquid that may have a pink tint. It is supplied as follows:

Package of 1 individually pouched single-dose tube.

Package of 10 individually pouched single-dose tubes.

The plastic tube and cap are not made with natural rubber latex.

17.1 Storage and Handling

Store and transport refrigerated at 2-8°C. RotaTeq should be administered as soon as possible after being removed from refrigeration. Protect from light.

RotaTeq should be discarded in approved biological waste containers according to local regulations.

The product must be used before the expiration date. The expiry date of the product is indicated on the packaging materials.

18 LICENSE HOLDER AND IMPORTER

Merck Sharp & Dohme (Israel - 1996) Company Ltd., 34 Ha'charash St., Hod-Hasharon.

Drug registration no. listed in the official Registry of the Ministry of Health:

136-76-31569

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