

PRODUCT INFORMATION

RotaTeq[®]
(rotavirus vaccine, live, oral, pentavalent, MSD)

DESCRIPTION

RotaTeq is a live, oral pentavalent reassortant vaccine for use in the prevention of rotavirus gastroenteritis.

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

G1	2.2 X 10 ⁶ infectious units
G2	2.8 X 10 ⁶ infectious units
G3	2.2 X 10 ⁶ infectious units
G4	2.0 X 10 ⁶ infectious units
P1[8]	2.3 X 10 ⁶ infectious units

The reassortants are propagated in Vero cells using standard tissue 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 and also culture media. There are no preservatives or thiomersal present.

RotaTeq is a pale yellow clear liquid that may have a pink tint.

CLINICAL PHARMACOLOGY

Rotavirus is the leading cause of severe acute gastroenteritis in infants and young children, with potentially severe consequences including hospitalisation and death. The greatest proportion of hospitalisations occurs among infants and young children between 6 months and 23 months of age. If left untreated without prompt oral or intravenous administration of fluids, rotavirus gastroenteritis may cause dehydration that is fatal.

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 over 90% of rotavirus disease in North America, Europe, and Australia and over 88% of rotavirus disease worldwide between 1973 and 2003. The proportion of circulating rotavirus serotypes varies from year to year. 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).

CLINICAL TRIALS

Efficacy

Overall, 71,942 infants were randomised 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 vaccinated 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 (mild, moderate, and severe) of rotavirus gastroenteritis and 2) Efficacy against severe rotavirus gastroenteritis (see Table 1). The efficacy was also demonstrated by a reduction in health care utilisation. Hospitalisation and emergency department visits for rotavirus were evaluated among all 68,038 subjects vaccinated in REST. The effect of the vaccine on physician office visits for rotavirus was evaluated among a subset of 5,673 subjects. 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 all 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, diarrhoea, 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 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 protection against non-vaccine G-serotypes that may contain P1[8]. The efficacy against any severity of gastroenteritis caused by the non-vaccine G serotype (G9) was 74.1%, which was not a statistically significant effect as there were small numbers of cases. See Table 1. However, when the reductions in hospitalisations and emergency department visits were examined for non-vaccine serotype G9, the reductions were found to be statistically significant (see Table 3).

Table 1

Efficacy of RotaTeq against rotavirus gastroenteritis through the first full rotavirus season after completion of vaccination

Rotavirus Gastroenteritis Cases by Severity	(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, 100.0)*

* Statistically Significant

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

RotaTeq reduced health care contacts through the prevention of hospitalisations, emergency department visits, and non-urgent visits for rotavirus gastroenteritis as shown in Tables 2 and 3.

Table 2

Number of Health Care Contacts and Rate Reductions for Rotavirus Gastroenteritis Caused by the G-serotypes Included in the Vaccine

Type of Health Care Contact	RotaTeq	Placebo	% Rate Reduction and 95% CI
Combined Endpoint (Hospitalisations and Emergency Department Visits)*	20	369	94.5 (91.2, 96.6)
Hospitalisations	6	144	95.8 (90.5, 98.2)
Emergency Department Visits	14	225	93.7 (88.8, 96.5)
Non-Urgent Visits**	13	98	86.0 (73.9, 92.5)

*N=68,038 infants vaccinated

**N=5,673 infants vaccinated

Table 3

Number of Hospitalisations and Emergency Department (ED) Visits for Rotavirus Gastroenteritis According to the G Serotype Identified in the Subject's Stool in REST

Serotype	Number of Hospitalisations and ED Visits for Rotavirus Gastroenteritis		% Rate Reduction (95% CI)
	RotaTeq (N=34,035)	Placebo (N=34,003)	
G1	16	328	95.1 (91.6, 97.1)*
G2	1	8	87.6 (<0, 98.5)
G3	1	15	93.4 (49.4, 99.1)*
G4	2	18	89.1 (52.0, 97.5)*
G9	0	13	100 (67.4, 100)*

* Statistically significant

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

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 postvaccination was 62.6% (see Table 4). The efficacy of RotaTeq beyond the second season postvaccination was not evaluated.

Table 4

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.

	(Number of cases / Number of evaluable subjects)		% Efficacy (95% CI)
	RotaTeq	Placebo	
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. The efficacy of RotaTeq was evaluated among a subset of 204 pre-term infants who were followed for gastroenteritis. Efficacy (70.3%) in the subset of 204 pre-term infants (153 evaluable) was generally similar to the efficacy in the overall population (see Table 5).

Table 5

Efficacy of RotaTeq in pre-term infants against any severity of rotavirus gastroenteritis caused by the G-serotypes included in the vaccine through the first rotavirus season after completion of vaccination

	(Number of cases / Number of evaluable subjects)		% Efficacy
	RotaTeq	Placebo	
Rotavirus Gastroenteritis Cases	3/75	10/78	70.3 (<0, 94.7)

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 6). 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 6

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 paediatric vaccines

	(Number of cases / Number of evaluable subjects)		% Efficacy
	RotaTeq	Placebo	
Rotavirus Gastroenteritis Cases	1/602	10/637	89.5 (26.5, 99.8)

Immunogenicity

RotaTeq induces antibodies that neutralize 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. A relationship between antibody responses to RotaTeq and protection against rotavirus gastroenteritis has not yet been established.

INDICATIONS

RotaTeq is indicated for the prevention of rotavirus gastroenteritis (see Clinical Trials).

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.

PRECAUTIONS

No safety or efficacy data are available for the administration of RotaTeq to:

- immunocompromised patients such as
 - individuals with malignancies or who are otherwise immunocompromised;
 - individuals receiving immunosuppressive therapy; or
- 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 enrolment 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. There is a theoretical risk that the live virus vaccine can be transmitted to non-vaccinated contacts. Therefore, 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 diarrhoea or growth retardation 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.

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 level of protection provided by only one or two doses of RotaTeq was not studied in clinical trials.

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

Use in Pregnancy (Category B2)

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

Use in Lactation

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

Paediatric Use

Safety and efficacy have not been established in infants less than 6 weeks of age or in individuals older than 32 weeks of age. The first dose of vaccine should be administered by 12 weeks of age, and the vaccination course should be completed by 32 weeks of age. Safety, including the risk of intussusception, has not been studied in infants who received a vaccine dose after the age of 32 weeks. (See DOSAGE AND ADMINISTRATION for the recommended dosage schedule)

Interactions with Other Medicines

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

ADVERSE 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 7). 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 7
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 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 REST

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 diarrhoea and vomiting on a daily basis during the first week following each vaccination. Table 8 summarizes the frequencies of these adverse events, regardless of cause.

Table 8
Adverse Experiences of Special Clinical Interest within the First Week after the First Dose

Adverse Event	First Dose	
	RotaTeq	Placebo
Elevated Temperature ($\geq 100.5^{\circ}\text{F}$ [38.1 $^{\circ}\text{C}$] rectal equivalent)	17.1%	16.2%
Vomiting	6.7%	5.4%
Diarrhoea	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 ($\geq 1/10$); Common ($\geq 1/100$, $< 1/10$); Uncommon ($\geq 1/1,000$, $< 1/100$); Rare ($\geq 1/10,000$, $< 1/1,000$); Very Rare ($< 1/10,000$)

Infections and infestations

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

Gastrointestinal disorders

Very Common: diarrhoea (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 placebo-controlled studies. RotaTeq was well tolerated; the frequency of adverse experiences observed was generally similar to that seen when the concomitant vaccines were administered with placebo.

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 to infants.

The first dose of RotaTeq should be administered at 6 to 12 weeks of age; the subsequent doses at a minimum interval of 4 weeks. The third dose should be administered by 32 weeks of age (see PRECAUTIONS, Paediatric Use).

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.

Refer to the package insert for instructions on administration of the vaccine.

Use with Other Vaccines

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

The concomitant administration of RotaTeq and oral polio vaccine (OPV) has not been studied.

OVERDOSAGE

There are no data with regard to overdose.

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.

PRESENTATION

RotaTeq is available as a single, 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.

RotaTeq is supplied as :

- (1) a single-dose pre-filled dosing tube of vaccine.
- (2) a box of ten single-dose pre-filled dosing tubes of vaccine.

NAME AND ADDRESS OF SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
54-68 Ferndell Street, South Granville, 2142
NSW, Australia

NAME AND ADDRESS OF DISTRIBUTOR

CSL LIMITED
45 Poplar Road, Parkville, 3052
Victoria, Australia

POISON SCHEDULE

Prescription Only Medicine (Schedule 4)

This document was approved by the Therapeutic Goods Administration on 03 May 2006