Registration No.: 1C 9/55 (NB)

Importer / Manufacturer: MSD (Thailand) Ltd. / Merck Sharp & Dohme Corp., West Point, Pennsylvania 19486, USA

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICAL PRODUCT

RotaTeq®

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

3. PHARMACEUTICAL FORM

Solution for Oral Administration

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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.

4.2 Posology and method of administration

FOR ORAL USE ONLY. NOT FOR INJECTION.

<u>Posology</u>

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.

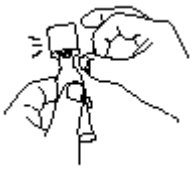
If for any reason an incomplete dose is administered (e.g., infant spits or regurgitates the vaccine), a replacement dose is not recommended, since such dosing was not studied in the clinical trials. The infant should continue to receive any remaining doses in the recommended series.

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

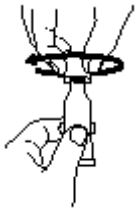
Each dose is supplied in a container consisting of a squeezable plastic, latex-free dosing tube with a twist-off cap, allowing for direct oral administration. The dosing tube is contained in a pouch.

To administer the vaccine:

Tear open the pouch and remove the dosing tube.

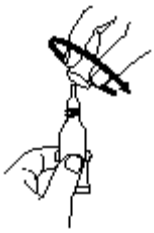


Clear the fluid from the dispensing tip by holding tube vertically and tapping cap.



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, meningococcal group C 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 reduce some immune responses to rotavirus vaccine, there is evidence that a high level of efficacy against severe rotavirus gastroenteritis is maintained. The immune responses to RotaTeq are unaffected when OPV is administered two weeks after RotaTeq.

4.3 Contraindication

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.

4.4 Special warnings and precautions for use

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 X. SIDE EFECTS, *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.

4.5 Interaction with other medical products and forms of interaction

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

4.6 Pregnancy and lactation

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.

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.

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 IV. DOSAGE AND ADMINISTRATION for the recommended dosage schedule.)

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

4.7 Effects on the ability to drive and use machines

N/A

4.8 Undesirable 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 I). 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 I
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 II summarizes the frequencies of these adverse events, regardless of cause.

Table II
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 subsequent controlled studies, the safety and immunogenicity of RotaTeq when administered concomitantly with oral poliovirus vaccine, meningococcal group C conjugate vaccine, or hexavalent vaccine were evaluated. In all these studies, concomitant use with these vaccines 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 with vaccine viral shedding in infants with Severe Combined Immunodeficiency Disease (SCID), 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 V. PRECAUTIONS.)

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

N/A

5.2 Pharmacokinetic properties

N/A

5.3 Preclinical safety data

N/A

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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.

DNA fragments from porcine circoviruses (PCV) 1 and 2 have been detected in RotaTeq. The source is porcine-derived material used in the manufacture of the vaccine. PCV-1 and PCV-2 are not known to cause disease in humans.

6.2 Incompatibilities

N/A

6.3 Shelf life

24 months

6.4 Special precautions for 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.

6.5 Nature and content of container

RotaTeq is available as a single, pre-filled 2 mL unit dose in a plastic dosing tube with a twist-off cap in boxes containing 1 or 10 dosing tube. The dosing tube is contained in a pouch. The container and delivery system are latex-free.

6.6 Special precautions for disposal and other handling

N/A

7. MARKETING AUTHORISATION HOLDER

MSD (Thailand) Ltd.

Bangkok, Thailand

8. MARKETING AUTHORISATION NUMBER(S)

1C 9/55 (NB)

9. DATE OF FIRST AUTHORAISATION/RENEWAL OF THE AUTHORISATION

17-Apr-2012

10. DATE OF REVISION OF THE TEXT

Jun-2013