SG-V260-OS-082016

PRODUCT CIRCULAR

Solution for Oral Administration Only and Should Not Be Injected.

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

I. THERAPEUTIC CLASS

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

II. CLINICAL PHARMACOLOGY

Pharmacodynamics/Pharmacokinetics

Mechanism of Action

Protection from natural rotavirus infection is largely serotype specific. The human rotavirus serotypes (G1, G2, G3, G4, and P1A[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).

There is no pharmacokinetic data for this product.

Efficacy

The protective efficacy of RotaTeq was evaluated in two ways:

1. The efficacy of RotaTeq for prevention of rotavirus gastroenteritis was evaluated among 6,983 infants who received vaccine (n=3,484) or placebo (n=3,499) in 2 studies: the Rotavirus Efficacy and Safety Trial (REST) and Study 007. Efficacy evaluations included efficacy against any severity of rotavirus gastroenteritis and efficacy against severe rotavirus gastroenteritis.

2. The reduction in health care contacts for rotavirus gastroenteritis, including hospitalizations and emergency department visits, 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 post-vaccination 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 third dose of vaccine or placebo was administered to infants as old as 32 weeks of age. Concomitant administration of other licensed childhood vaccines except for oral poliovirus vaccine (OPV) was permitted in all Phase III studies.

Efficacy against any severity of gastroenteritis caused by naturally occurring rotavirus of the composite of the G serotypes (G1-G4) included in the vaccine was 73.8%, and efficacy against severe rotavirus gastroenteritis was 98.2% through the first rotavirus season after completion of vaccination. The type specific vaccine efficacy observed against rotavirus gastroenteritis was 75.0% for G1 serotype. RotaTeq also provided protection against non-vaccine G serotypes. Based on limited data, 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. The efficacy of RotaTeq (among a subset of 4,451 evaluable infants) through two rotavirus seasons after completion of vaccination against any severity of rotavirus gastroenteritis was 71.3%.

RotaTeq reduced the rate of hospitalizations, emergency department visits, non-urgent care visits, and parent/legal guardian work loss days. The rate reductions for health care contacts (hospitalizations and emergency department visits) caused by serotypes G1-G4 in REST and the Extension study combined were as follows:

- 94.4% for hospitalizations and emergency department visits (RotaTeq n=34,035 infants, placebo n=34,003 infants);

- 94.3% for hospitalizations; and
- 94.4% for emergency department visits.

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 2 years after vaccination in REST. The rate reductions were as follows:

- 86.0% for non-urgent care visits (RotaTeq n=2,834, placebo n=2,839 infants); and
- 86.6% for parent/legal guardian work loss days (RotaTeq n=34,035 infants, placebo n=34,003 infants).

Efficacy of RotaTeq against rotavirus gastroenteritis through the first full rotavirus season after completion of vaccination and reduction in hospitalizations and emergency department visits for rotavirus gastroenteritis for up to 3 years postvaccination by G-serotype are shown in Table 1.

Table 1

Efficacy of RotaTeq against rotavirus gastroenteritis

Reduction in incidence of rotavirus gastroenteritis through one full season post-vaccination in REST and Study 007 (RotaTeq n=3,484*) (% [95% CI])						
		Efficacy against any severity by rotavirus serotype				
Severe disease (G1-G4)	Any severity (G1-G4)	G1	G2	G3	G4	G9
98.2% [89.6, 100]†	73.8% [67.2, 79.3]†	75.0% [68.2, 80.5]†	63.4% [2.7, 88.2]†	55.6% [<0, 92.6]	48.1% [<0, 91.6]	74.1% [<0, 99.5]

Reduction in hospitalisations and emergency department visits for rotavirus gastroenteritis for up to 2 years post-vaccination in REST and for up to 3 years post-vaccination in the Extension study** (RotaTeq n=34,035*) (% [95% CI])					
G1-G4	G1	G2	G3	G4	G9
94.4%	95.5%	81.9%	89.0%	83.4%	94.2%

[91.6, 96.2]†	[92.8, 97.2]†	[16.1, 98.0]†	[53.3, 98.7]†	[51.2, 95.8]†	[62.2, 99.9]†

* n= Number Vaccinated

† Statistically Significant

** 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 2.

Table 2

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]

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 hospitalisations and emergency department visits for rotavirus

gastroenteritis during administration of the 3-dose vaccination series starting from 14 days post dose 1.

Efficacy and Safety in Pre-term Infants

RotaTeq or placebo was administered to 2,070 pre-term infants (25 to 36 weeks gestational age), including 1,007 recipients of RotaTeq, according to their chronological age in a placebo-controlled study. Among a subset of 308 pre-term infants who were followed for all adverse experiences, the safety profile was generally similar among those infants receiving RotaTeq as compared with those receiving placebo. The incidence of fever, vomiting, diarrhea, or irritability was generally similar among vaccine and placebo recipients.

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]. 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].

Effectiveness

The results of the three post-licensure vaccine effectiveness studies presented in Table 3 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 3

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

Study	Study population	Endpoints	Effectiveness	RV seasons

design (Region)			% [95%CI]	
Claims database analysis (US)*	33,140 vaccinated 26,167 unvaccinated Aged ≥ 7 months Received 3 doses	Hospitalisation and Emergency Department (ED) visits due to RVGE† Outpatient visits due to RVGE Hospitalisation and ED visits due to all-cause gastroenteritis	100% [87,100] 96% [76,100] 59% [47,68]	2007-2008
Cohort study (France)‡	1,895 vaccinated with 3 doses 2,102 unvaccinated Aged <2 years	Hospitalisation 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

Studies with Other Vaccines

The immunogenicity of RotaTeq and diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine, inactivated poliovirus vaccine (IPV), *Haemophilus influenzae* type b conjugate vaccine (Hib), hepatitis B vaccine, and pneumococcal conjugate vaccine was evaluated among 1,358 infants. The immune responses to the specified vaccines were unaffected by RotaTeq. In addition, the studies demonstrated the efficacy of RotaTeq (89.5%) when administered with these vaccines.

Concomitant administration of RotaTeq and oral polio vaccine (OPV) did not affect the immune response to the polio antigens in a controlled study of 735 vaccinated infants. Although concomitant administration of OPV reduced some of the immune responses to RotaTeq, the seroresponse rates (≥ 3-fold rise from baseline) for serum anti-rotavirus IgA were > 93%. The immune responses to RotaTeq are unaffected when OPV is administered two weeks after RotaTeq.

The safety profile, including the incidences of fever, vomiting, diarrhea, and irritability, was generally similar among subjects receiving the specified concomitant vaccines with RotaTeq and subjects receiving the specified concomitant vaccines with placebo.

In one study, 7,367 infants received a hexavalent (DTaP, IPV, HIB, and hepatitis B) vaccine concomitantly with RotaTeq. The frequency of overall serious adverse experiences (SAEs), regardless of causal relationship, was 2.9% in recipients of RotaTeq and 3.2% in placebo recipients. More detailed safety information was evaluated among a subset of 638 infants receiving RotaTeq with a hexavalent vaccine. The safety profile, including the incidences of fever, vomiting, diarrhea, and irritability, was generally similar among subjects receiving a hexavalent vaccine with RotaTeq and subjects receiving a hexavalent vaccine with placebo. In a subsequent randomized, double-blinded, placebo-controlled multicenter immunogenicity and safety trial among 403 healthy infants, concomitant administration of RotaTeq with a hexavalent vaccine did not interfere with the serum antibody responses or seroprotection rates to any of the antigens in the hexavalent vaccine or RotaTeq. Concomitant administration of RotaTeq and the hexavalent vaccine was well tolerated.

An open-label, randomized, comparative, multicenter study of the immunogenicity and safety of the concomitant use of RotaTeq and a meningococcal group C conjugate vaccine was conducted among 246 healthy infants. Concomitant administration did not affect the immune response to either vaccine, and both vaccines were well tolerated.

Immunogenicity

The immunologic mechanism by which RotaTeq protects against rotavirus gastroenteritis is unknown. A relationship between antibody responses to RotaTeq and protection against rotavirus gastroenteritis has not been established. In phase III studies, 92.9% to 100% of 372 recipients of RotaTeq achieved a 3-fold or more rise in serum anti-rotavirus IgA after a three-dose regimen when compared to 12.5% to 20.0% of 324 placebo recipients.

III. INDICATIONS

RotaTeq is an oral pentavalent vaccine indicated for the prevention of severe rotavirus gastroenteritis in infants and children (See II. CLINICAL PHARMACOLOGY section).

IV. 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. The third dose should not be administered after 32 weeks of age (See IX. PEDIATRIC 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.

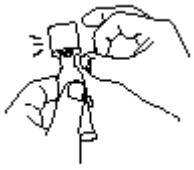
If for any reason an incomplete dose is administered (e.g., infant spits or regurgitates the vaccine), a replacement dose is not recommended, since such dosing was not studied in the clinical trials. The infant should continue to receive any remaining doses in the recommended series.

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

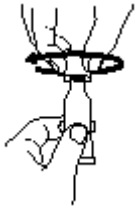
Each dose is supplied in a container consisting of a squeezable plastic, latex-free dosing tube with a twist-off cap, allowing for direct oral administration. The dosing tube is contained in a pouch.

To administer the vaccine:

Tear open the pouch and remove the dosing tube.

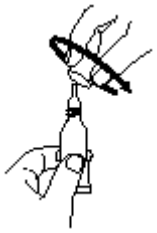


Clear the fluid from the dispensing tip by holding tube vertically and tapping cap.



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, but may reduce that to RotaTeq. The immune responses to RotaTeq are unaffected when OPV is administered two weeks after RotaTeq.

V. CONTRAINDICATIONS

The administration of RotaTeq should be postponed in subjects suffering from acute diarrhea or vomiting.

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.

Subjects with congenital malformation of the gastrointestinal tract.

Infants who have known or suspected immunodeficiency. Asymptomatic HIV infection is not expected to affect the safety or efficacy of RotaTeq. However, in the absence of sufficient data, administration of RotaTeq to asymptomatic HIV subjects is not recommended.

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

Previous history of intussusception.

VI. PRECAUTIONS

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

Prior to administration of this vaccine, health care personnel should inform the parent or guardian of the benefits and risks to the vaccinee, and the importance of completing the immunization series. Parents and guardians should be instructed to report any serious adverse reactions to their health care provider.

It is good clinical practice that vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

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.

No increased risk of intussusception was observed in clinical trials following administration of RotaTeq when compared with placebo.

However, in worldwide post-marketing experience, cases of intussusception have been reported in temporal association with RotaTeq, mostly within 7 days post dose 1 (See XII. SIDE EFFECTS, *Post-marketing Reports*.).

Therefore, as a precaution, healthcare professionals should follow-up on any symptoms suggestive of intussusception (severe abdominal pain or distress, persistent vomiting, bloody stools, abdominal bloating and/or high fever). Parents/guardians should be advised to seek medical advice promptly where these signs/symptoms are evident.

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.

The level of protection provided by RotaTeq is based on the completion of all 3 doses. As with any vaccine, vaccination with RotaTeq may not result in complete protection in all recipients. RotaTeq does not protect against gastroenteritis due to other pathogens than rotavirus.

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

The clinical studies were not designed to assess the level of protection provided by only 1 or 2 doses of RotaTeq.

RotaTeq SHOULD NOT BE INJECTED.

VII. 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.

VIII. 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.

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

X. DRUG INTERACTIONS

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

XI. CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

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

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 4). 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 4

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 5 summarizes the frequencies of these adverse events, regardless of cause.

Table 5

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 polio 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.

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.

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.

Gastrointestinal:

Intussusception

Hematochezia

Gastroenteritis with vaccine viral shedding in infants with Severe Combined Immunodeficiency Disease (SCID).

Skin and subcutaneous tissue disorders: urticaria, angioedema.

Post-Marketing Observational Safety Surveillance Studies

The temporal association between vaccination with RotaTeq and intussusception was evaluated in several studies worldwide.

Some studies in the US did not show a statistically significant increased risk of intussusception in any period after vaccination. In one of these studies, a large prospective post-marketing

observational study in the US, the risks of intussusception or Kawasaki disease were analyzed among 85,150 infants receiving one or more doses of RotaTeq (17,433 person-years of follow-up).

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 compared with a concurrent control group of infants who received DTaP, but not RotaTeq (n=62,617, 12,339 person-years of follow-up). For intussusception, 6 confirmed cases were recorded 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). For Kawasaki disease, one chart-confirmed case was recorded among infants vaccinated with RotaTeq compared with one chart-confirmed case among concurrent DTaP controls (relative risk = 0.7, 95% CI: 0.01-55.56). In the general safety analyses, no specific safety concerns were identified (See VI. PRECAUTIONS).

In studies showing an increased risk of intussusception associated with rotavirus vaccination, conducted in the US and Australia, the attributable risk was approximately 1 to 1.5 excess cases in the US and 6 excess cases in Australia of intussusception per 100,000 vaccinees within 21 days following vaccination. The background incidence of intussusception [in infants less than one year of age] in these countries ranged from 33 to 101 per 100,000 infants per year. It remains unclear whether rotavirus vaccines affect the overall incidence of intussusception based on longer periods of follow up.

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. 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 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.

XV. COMPOSITION

Each 2 mL dose contains the following human-bovine rotavirus reassortants: G1, G2, G3, G4, and P1A[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

P1A[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.

XVI. AVAILABILITY

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.

Not all presentations may be available locally.

Product Owner:

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