ROTAVIRUS VACCINE, LIVE, ORAL, PENTAVALENT

RotaTeq™
Solution for Oral Administration

THERAPEUTIC CLASS

ROTAVIRUS VACCINE, LIVE, ORAL, PENTAVALENT hereafter referred to as PENTAVALENT ROTAVIRUS VACCINE (RotaTeq), is a live, oral pentavalent vaccine which protects against rotavirus gastroenteritis.

INDICATIONS

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

DOSAGE AND ADMINISTRATION

FOR ORAL USE ONLY.  NOT FOR INJECTION.

Posology
The vaccination series consists of three ready-to-use liquid doses of PENTAVALENT ROTAVIRUS VACCINE, (RotaTeq) administered orally to infants.

The first dose of PENTAVALENT ROTAVIRUS VACCINE (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 PENTAVALENT ROTAVIRUS VACCINE (RotaTeq).

PENTAVALENT ROTAVIRUS VACCINE (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.

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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:

1. Tear open the pouch and remove the dosing tube.
2. Clear the fluid from the dispensing tip by holding tube vertically and tapping cap.
3. 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.
4. 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.)
5. Discard the empty tube and cap in approved biological waste containers according to local regulations.

Use with Other Vaccines

PENTAVALENT ROTAVIRUS VACCINE (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 PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) and oral polio 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 PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) are unaffected when OPV is administered two weeks after PENTAVALENT ROTAVIRUS VACCINE (RotaTeq).

**CONTRAINDICATIONS**

Hypersensitivity to any component of the vaccine.

Individuals who develop symptoms suggestive of hypersensitivity after receiving a dose of PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) should not receive further doses of PENTAVALENT ROTAVIRUS VACCINE (RotaTeq).

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

**PRECAUTIONS**

No safety or efficacy data are available from clinical trials regarding the administration of PENTAVALENT ROTAVIRUS VACCINE (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 PENTAVALENT ROTAVIRUS VACCINE (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, PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) was not administered to infants known to have immunodeficient household members. In these trials, PENTAVALENT ROTAVIRUS VACCINE (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. PENTAVALENT ROTAVIRUS VACCINE (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 PENTAVALENT ROTAVIRUS VACCINE (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 PENTAVALENT ROTAVIRUS VACCINE (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 PENTAVALENT ROTAVIRUS VACCINE, (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 PENTAVALENT ROTAVIRUS VACCINE (RotaTeq).

As with any vaccine, vaccination with PENTAVALENT ROTAVIRUS VACCINE (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 PENTAVALENT ROTAVIRUS VACCINE (RotaTeq). Post hoc analyses of data from a large clinical study suggest that PENTAVALENT ROTAVIRUS VACCINE (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 PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) when administered after exposure to rotavirus.

PREGNANCY

PENTAVALENT ROTAVIRUS VACCINE (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 PENTAVALENT ROTAVIRUS VACCINE (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

PENTAVALENT ROTAVIRUS VACCINE (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 DOSAGE AND ADMINISTRATION for the recommended dosage schedule.)

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

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

SIDE EFFECTS

71,725 infants were evaluated in 3 placebo-controlled clinical trials including 36,165 infants who received PENTAVALENT ROTAVIRUS VACCINE (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 Rotavirous Efficacy and Safety Trial (REST), PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) did not increase the risk of intussusception relative to placebo (see Table 1). 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>
<thead>
<tr>
<th>Table 1</th>
<th>Confirmed Cases of Intussusception in Recipients of PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) as Compared with Placebo Recipients during REST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PENTAVALENT ROTAVIRUS VACCINE (RotaTeq™) (n=34,837)</td>
</tr>
<tr>
<td>Confirmed intussusception cases within 42 days after each dose</td>
<td>6</td>
</tr>
<tr>
<td>Relative Risk (95% CI)†</td>
<td>1.6 (0.4, 6.4)</td>
</tr>
<tr>
<td>Confirmed intussusception cases within 365 days after dose one</td>
<td>13</td>
</tr>
<tr>
<td>Relative Risk (95% CI)</td>
<td>0.9 (0.4, 1.9)</td>
</tr>
</tbody>
</table>

† 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 PENTAVALENT ROTAVIRUS VACCINE (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 2 summarizes the frequencies of these adverse events, regardless of cause.

Table 2
Adverse Experiences of Special Clinical Interest within the First Week after the First Dose

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>First Dose</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PENTAVALENT ROTAVIRUS VACCINE (RotaTeq)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated Temperature (≥100.5°F [38.1°C] rectal equivalent)</td>
<td>17.1%</td>
<td>16.2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6.7%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10.4%</td>
<td>9.1%</td>
</tr>
</tbody>
</table>

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 PENTAVALENT ROTAVIRUS VACCINE (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 PENTAVALENT ROTAVIRUS VACCINE (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 PENTAVALENT ROTAVIRUS VACCINE (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.

Safety in Pre-term Infants

Vaccine safety was generally comparable to that in the REST study population as a whole.

Post-marketing Reports

The following adverse experiences have been spontaneously reported during post-approval use of PENTAVALENT ROTAVIRUS VACCINE (Rot aTeq). 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.

Skin and subcutaneous tissue disorders: urticaria.

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

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 PENTAVALENT ROTAVIRUS VACCINE (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 PENTAVALENT ROTAVIRUS VACCINE (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 PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) (n=62,617). There were 6 confirmed cases of intussusception among infants vaccinated with PENTAVALENT ROTAVIRUS VACCINE (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 PENTAVALENT ROTAVIRUS VACCINE (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.
Rotavirus is the leading cause of severe acute gastroenteritis in infants and young children in industrialized and developing countries. Rotavirus gastroenteritis is a universal disease affecting over 95% of infants and young children by the time they are 5 years old, regardless of their socioeconomic status or environmental conditions. Worldwide it is estimated that 138 million children develop rotavirus gastroenteritis each year which results in 25 million clinic visits, 2.1 million hospitalizations and 352,000 to 592,000 deaths. In the US it is estimated that 3.5 million children develop rotavirus gastroenteritis each year which results in 500,000 physician office visits, 55,000 hospitalizations, and 20 to 102 deaths. One out of every 8 children will seek care from a physician and one out of every 73 children will be hospitalized for rotavirus gastroenteritis in the US by the time they are 5 years old. The greatest proportion of hospitalizations occurs among infants and young children between 6 months and 24 months of age. If left untreated without prompt oral or intravenous administration of fluids, rotavirus gastroenteritis may cause dehydration that is fatal.

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

Mechanism of Action

Protection from natural rotavirus infection is largely serotype specific. The human rotavirus serotypes (G1, G2, G3, G4, and P1A[8]) have been selected for PENTAVALENT ROTAVIRUS VACCINE (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 PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) protects against rotavirus gastroenteritis is unknown. Studies suggest a combination of factors is important in rotavirus immunity including neutralizing antibodies to the outer capsid G proteins, serum and secretory IgA, and other local mucosal responses (see Immunogenicity).

Efficacy

Overall, 71,942 infants were randomized worldwide in 3 placebo-controlled phase III studies. The data demonstrating the efficacy of PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) in preventing rotavirus gastroenteritis come from 6,983 of these infants from the US (including Navajo and White Mountain Apache Nations) and Finland who were enrolled in 2 of these studies: the Rotavirus Efficacy and Safety Trial (REST) and Study 007. The efficacy evaluations in these studies included: 1) Efficacy against any severity of rotavirus gastroenteritis and 2) Efficacy against severe rotavirus gastroenteritis (see Table 3). The effect on health care contacts for rotavirus gastroenteritis, including hospitalizations and emergency department visits, was also evaluated among the 68,038 infants enrolled in REST and in a subset of 20,736 infants in the Extension study among the Finnish cohort of REST. The infants were followed for up to 2 years in REST and those in the Extension study continued to be followed for up to 3 years post-vaccination. No safety data were collected during the Extension study. The reductions in routine visits to a physician and parent/legal guardian work loss days were also evaluated in REST. The first dose was administered between 6 and 12 weeks of age and subsequent doses were to be given at 4- to 10-week intervals. The third dose was administered to infants as old as 32 weeks of age. Breast-feeding and concomitant administration of other
licensed childhood vaccines except for oral poliovirus vaccine (OPV) were permitted in these studies. As Table 3 shows, PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) was efficacious against rotavirus gastroenteritis of any severity and severe rotavirus gastroenteritis. The efficacy analyses include cases that occurred at least 14 days after the third dose. Severe gastroenteritis is defined as a numerical score of >16 points on a 24-point scale. The scoring system evaluates the clinical manifestations of rotavirus gastroenteritis taking into account the duration and intensity of fever, vomiting, diarrhea, and behavioral changes. The scoring system has been validated to correlate with physician-assessment of the intensity of these signs and symptoms.

Efficacy through the first rotavirus season after vaccination against severe rotavirus gastroenteritis caused by naturally occurring rotavirus of the composite of the G serotypes included in the vaccine (G1-G4) was 98.2%, and efficacy against any severity of rotavirus gastroenteritis was 73.8%. The vaccine was specifically designed to prevent rotavirus gastroenteritis caused by the individual G-serotypes included in the vaccine (G1, G2, G3, and G4); P1A[8] was included in the vaccine to potentially provide cross-protection against non-vaccine G-serotypes that may contain P1A[8]. Based on limited data, the efficacy against any severity of gastroenteritis caused by the non-vaccine G serotype (G9) was 74.1%. Efficacy of PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) against rotavirus gastroenteritis by G-serotype is shown in Table 3.

Table 3

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Number of cases / Number of evaluable subjects</th>
<th>% Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PENTAVALENT ROTAVIRUS VACCINE (RotaTeq)</td>
<td>Placebo</td>
</tr>
<tr>
<td>Any Severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1-G4</td>
<td>97/2,758</td>
<td>369/2,869</td>
</tr>
<tr>
<td>G1</td>
<td>85/2,757</td>
<td>339/2,860</td>
</tr>
<tr>
<td>G2</td>
<td>6/2,755</td>
<td>17/2,856</td>
</tr>
<tr>
<td>G3</td>
<td>3/2,754</td>
<td>7/2,850</td>
</tr>
<tr>
<td>G4</td>
<td>3/2,754</td>
<td>6/2,850</td>
</tr>
<tr>
<td>G9</td>
<td>1/2,754</td>
<td>4/2,849</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1-G4</td>
<td>1/2,747</td>
<td>57/2,834</td>
</tr>
</tbody>
</table>

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

PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) reduced the rate of hospitalizations, emergency department visits, non-urgent care visits, and parent/legal guardian work loss days. The reduction in hospitalizations and emergency department visits for rotavirus gastroenteritis caused by serotypes G1-G4 was evaluated among 68,038 infants in REST and in a subset of 20,736 infants in the Extension study among the Finnish cohort of REST. The infants were followed for up to 2 years in REST and those in the Extension study continued to be followed for
up to 3 years post-vaccination. During year 3 (PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) n=3,112 infants, placebo n=3,126 infants), there were no health care contacts for rotavirus gastroenteritis in the vaccine group and there was 1 (non-typeable) in the placebo group. Non-urgent care visits and parent/legal guardian work loss days were evaluated for up to two years after vaccination in REST. The rate reductions for health care contacts are shown in Table 4.

Table 4
Number of health care contacts and rate reductions for rotavirus gastroenteritis caused by the G-serotypes included in the vaccine in REST and the Extension study combined

<table>
<thead>
<tr>
<th>Type of Health Care Contact</th>
<th>PENTAVALENT ROTAVIRUS VACCINE (RotaTeq)</th>
<th>Placebo</th>
<th>% Rate Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined Endpoint (Hospitalizations and Emergency Department Visits)*</td>
<td>28</td>
<td>493</td>
<td>94.4 (91.6, 96.2)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>13</td>
<td>226</td>
<td>94.3 (89.9, 97.0)</td>
</tr>
<tr>
<td>Emergency Department Visits</td>
<td>15</td>
<td>267</td>
<td>94.4 (90.5, 96.9)</td>
</tr>
<tr>
<td>Non-Urgent Visits**</td>
<td>13</td>
<td>98</td>
<td>86.0 (73.9, 92.5)</td>
</tr>
</tbody>
</table>

*N=68,038 infants vaccinated, follow-up for up to 2 years in REST and for up to 3 years in the Extension study. There were no typeable episodes of rotavirus gastroenteritis leading to hospitalizations or emergency department visits for rotavirus gastroenteritis in year 3. **N=5,673 infants vaccinated, follow-up for up to 2 years in REST

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

The reduction in hospitalizations and emergency department visits for rotavirus gastroenteritis by serotype identified in stool in REST and the Extension study is shown in Table 5.

Table 5
Reduction in the numbers of hospitalizations and/or emergency department visits by G-serotype in stool for up to 2 years after vaccination in REST and for up to 3 years post-vaccination in the Extension study*

<table>
<thead>
<tr>
<th>Serotype</th>
<th>PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) (N=34,035)</th>
<th>Placebo (N=34,003)</th>
<th>Percent Rate Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>20</td>
<td>440</td>
<td>95.5 (92.8, 97.2)</td>
</tr>
<tr>
<td>G2</td>
<td>2</td>
<td>11</td>
<td>81.9 (16.1, 98.0)</td>
</tr>
<tr>
<td>G3</td>
<td>2</td>
<td>18</td>
<td>89.0 (53.3, 98.7)</td>
</tr>
<tr>
<td>G4</td>
<td>4</td>
<td>24</td>
<td>83.4 (51.2, 95.8)</td>
</tr>
<tr>
<td>G9</td>
<td>1</td>
<td>17</td>
<td>94.2 (62.2, 99.9)</td>
</tr>
</tbody>
</table>
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 PENTAVALENT ROTAVIRUS VACCINE (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 PENTAVALENT ROTAVIRUS VACCINE (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 6.

### Table 6

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

<table>
<thead>
<tr>
<th>PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) n=34,035 infants; Placebo n=34,003 infants</th>
<th>From ≥14 days after dose 1 until dose 2</th>
<th>From 14 ≥days after dose 2 until dose 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotype</td>
<td>G1-G4</td>
<td>G1-G4</td>
</tr>
<tr>
<td>Efficacy estimate % and [95% confidence interval]</td>
<td>100 [72.2, 100]</td>
<td>90.9 [62.9, 99.0]</td>
</tr>
</tbody>
</table>

**Efficacy through Multiple Rotavirus Seasons**

The efficacy of PENTAVALENT ROTAVIRUS VACCINE (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 PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) in preventing cases occurring only during the second rotavirus season postvaccination was 62.6% (see Table 7).
Table 7
Efficacy of PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) against any severity of rotavirus gastroenteritis caused by the G-serotypes included in the vaccine for the second rotavirus season after vaccination.

<table>
<thead>
<tr>
<th>PENTAVALENT ROTAVIRUS VACCINE (RotaTeq)</th>
<th>Placebo</th>
<th>% Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases / Number of evaluable subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotavirus gastroenteritis cases occurring through the first and second seasons</td>
<td>118/2,173</td>
<td>403/2,278</td>
</tr>
<tr>
<td>Rotavirus gastroenteritis cases occurring during the second season only</td>
<td>36/813</td>
<td>88/756</td>
</tr>
</tbody>
</table>

Safety and Efficacy in Pre-term Infants

PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) was generally well tolerated and prevented rotavirus gastroenteritis in infants born prematurely. PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) or placebo was administered to 2,070 pre-term infants (25 to 36 weeks gestational age) according to their chronological age in a placebo-controlled study. In a subset of 204 vaccinated infants (99 in the vaccine group), protective efficacy, as measured by a reduction in the incidence of rotavirus gastroenteritis of any severity caused by vaccine serotypes (G1-G4) that occurred at least 14 days after the third dose of vaccine through the first full rotavirus season after vaccination, was 70.3 % [95 % CI <0, 94.7]. In 2,070 vaccinated infants (1,007 in the vaccine group) in REST, protective efficacy, as measured by a reduction in the rate of hospitalizations and emergency department visits for rotavirus gastroenteritis caused by G1-G4 from 14 days for up to 2 years after the third dose, was 100% [95 % CI 74, 100] (see Table 8). Likewise, the protective efficacy, as measured by a reduction in the rate of hospitalizations and emergency department visits for rotavirus gastroenteritis caused by any serotype from 14 days for up to 2 years after the third dose, was 100% [95% CI 82, 100].
Table 8

<table>
<thead>
<tr>
<th>Efficacy of PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) in pre-term infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in incidence of rotavirus gastroenteritis of any severity caused by the vaccine serotypes G1-G4 through one full season post-vaccination in REST</td>
</tr>
<tr>
<td>PENTAVALENT ROTAVIRUS VACCINE (RotaTeq)</td>
</tr>
<tr>
<td>Number of cases / Number of evaluable subjects</td>
</tr>
<tr>
<td>3/75</td>
</tr>
</tbody>
</table>

Reduction in hospitalizations and emergency department visits for rotavirus gastroenteritis caused by the serotypes G1-G4 for up to 2 years post-vaccination in REST

| PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) | Placebo | % Rate Reduction |
| Number of hospitalizations and emergency department visits / Number of evaluable subjects |
| 0/764 | 15/817 | 100 |

Safety, Efficacy, and Immunogenicity with Concomitant Administration of PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) and Other Vaccines

PENTAVALENT ROTAVIRUS VACCINE (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 9). The immune responses to the specified vaccines were unaffected by PENTAVALENT ROTAVIRUS VACCINE (RotaTeq).

Concomitant administration of PENTAVALENT ROTAVIRUS VACCINE (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 PENTAVALENT ROTAVIRUS VACCINE (RotaTeq), the seroresponse rates (≥3-fold rise from baseline) for serum anti-rotavirus IgA were > 93%. There is evidence that a high level of efficacy against severe rotavirus gastroenteritis is maintained. The immune responses to PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) are unaffected when OPV is administered two weeks after PENTAVALENT ROTAVIRUS VACCINE (RotaTeq).
Table 9
Efficacy of PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) against any severity of rotavirus gastroenteritis caused by the G-serotypes included in the vaccine in infants who received PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) concomitantly with other licensed pediatric vaccines

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>% Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PENTAVALENT ROTAVIRUS VACCINE (RotaTeq)</td>
<td>1/602</td>
<td>10/637</td>
</tr>
</tbody>
</table>

In a randomized, double-blinded, placebo-controlled multicenter immunogenicity and safety trial among 403 healthy infants, concomitant administration of PENTAVALENT ROTAVIRUS VACCINE (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 PENTAVALENT ROTAVIRUS VACCINE (RotaTeq). Concomitant administration of PENTAVALENT ROTAVIRUS VACCINE (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 PENTAVALENT ROTAVIRUS VACCINE (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**

A relationship between antibody responses to PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) and protection against rotavirus gastroenteritis has not yet been established. However, PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) induces antibodies that neutralize human serotypes G1, G2, G3, G4 and P1A[8]. In phase III clinical studies, 92.9% to 100% of recipients of PENTAVALENT ROTAVIRUS VACCINE (RotaTeq) achieved a significant rise in serum anti-rotavirus IgA after a three-dose regimen.

**OVERDOSAGE**

There have been reports of administration of higher than recommended doses of PENTAVALENT ROTAVIRUS VACCINE (RotaTeq). In general, the adverse event profile reported with overdose was comparable to that observed with recommended doses of PENTAVALENT ROTAVIRUS VACCINE (RotaTeq).
FORMULATION AND AVAILABILITY

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 \(2.2 \times 10^6\) infectious units
- G2 \(2.8 \times 10^6\) infectious units
- G3 \(2.2 \times 10^6\) infectious units
- G4 \(2.0 \times 10^6\) infectious units
- P1A[8] \(2.3 \times 10^6\) infectious units

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

PENTAVALENT ROTAVIRUS VACCINE (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.

STORAGE CONDITION

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

PENTAVALENT ROTAVIRUS VACCINE (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.

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without the prescription of a physician.