AUSTRALIAN PRODUCT INFORMATION

ROTATEQ® (Rotavirus vaccine, live, oral, pentavalent)

1 NAME OF THE MEDICINE

Rotavirus G1 human-bovine reassortant
Rotavirus G2 human-bovine reassortant
Rotavirus G3 human-bovine reassortant
Rotavirus G4 human-bovine reassortant
Rotavirus P1 [8] human-bovine reassortant

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each 2 mL dose of RotaTeq contains the following rotavirus reassortants: G1, G2, G3, G4, and P1A[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
P1A[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.

List of excipients with known effect: sucrose, sugars, benzoates, phenylalanine

For the full list of Excipients, see Section 6.1 List of Excipients.

The manufacture of this product includes exposure to bovine derived material. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

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.

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

RotaTeq is indicated for the prevention of rotavirus gastroenteritis (see Section 5.1 Pharmacodynamic Properties, Clinical trials).

4.2 DOSE AND METHOD OF 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 Section 4.4 Special Warnings and Precautions for Use, 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.

4.3 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.

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

Individuals with a history of intussusception.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Adequate treatment provisions, including adrenaline (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:

- immunocompromised patients such as
  - individuals with malignancies or who are otherwise immunocompromised;
  - individuals receiving immunosuppressive therapy;
- individuals infected with HIV; 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. 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 diarrhoea 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.

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 hospitalisations and emergency department visits for rotavirus gastroenteritis during administration of the 3-dose vaccination series starting from 14 days post dose 1 (see Section 5.1 Pharmacodynamic Properties, Clinical trials, Efficacy between doses).

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

In worldwide post-marketing surveillance, cases of intussusception have been reported in temporal association with RotaTeq [See Section 4.8 Adverse Effects (Undesirable Effects), Post-marketing reports].

Post-marketing safety data from Australia have identified an increased risk of intussusception shortly after the administration of the first dose and second dose of RotaTeq. No increased risk of intussusception was observed among infants receiving RotaTeq in two large post-marketing safety studies conducted in the United States. No increased risk of intussusception was observed in clinical trials following administration of RotaTeq compared with placebo. [See Section 4.8 Adverse Effects (Undesirable Effects)].

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.

Use in the elderly

RotaTeq is not indicated for use in adult populations.

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 Section 4.2 Dose and Method of Administration for the recommended dosage schedule).

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

There are no known drug interactions. (See Section 4.2 Dose and Method of Administration, Use with other vaccines.)

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Not applicable

4.8 ADVERSE EFFECTS (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 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 1
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

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 diarrhoea 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

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%
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 (≥ 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: 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 3 phase III, placebo-controlled studies. RotaTeq 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 Safety Surveillance Studies

Australian Case Series Analysis of Intussusception
A self-controlled, case-series analysis was undertaken in Australian infants immunised between July 2007 and June 2010 to evaluate cases of intussusception in the 21-day period following any vaccination with rotavirus vaccines. Data from this study indicated an increased relative risk of intussusception of 9.9 (95% CI 3.7 to 26.4, $p < 0.001$) and 6.3 (95% CI 2.8 to 14.4, $p < 0.001$) within 1-7 days and 8-21 days, respectively, following the first dose of RotaTeq. There was also some evidence of an elevated relative risk of 2.8 (95% CI 1.2 to 6.8, p=0.02) 1-7 days following dose 2 of RotaTeq. There was no indication of an increased risk following dose 3 of RotaTeq.

Whether RotaTeq affects the overall incidence of intussusception has not been established (see Section 4.4 Special Warnings and Precautions for Use). The overall incidence of intussusception remains rare.

These findings are not reflected in other post-marketing surveillance studies conducted in the U.S (see U.S. Post-Marketing Observational Safety Surveillance Study and U.S. Vaccine Safety Datalink Study).

U.S. Post-Marketing Observational Safety Surveillance Study
In a prospective post-marketing observational study conducted in the U.S. using a large medical claims database, the risks of intussusception or Kawasaki disease resulting in emergency department visits or hospitalisations 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 hospitalisations.

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 infants receiving RotaTeq (n=85,150, 17,433 person-years of follow-up) with a concurrent control group of infants who received DTaP, but not RotaTeq (n=62,617, 12,339 person-years of follow-up).

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, no specific safety concerns were identified. The results of these analyses were reviewed and confirmed by an independent, external Safety Monitoring Committee. (See Section 4.4 Special Warnings and Precautions for Use.)

U.S. Vaccine Safety Datalink Study
Another study in the U.S. was conducted by the Vaccine Safety Datalink (a collaboration between the Centers for Disease Control and Prevention and 8 managed care organizations). This study assessed the rate of intussusception in the 1-7 and 1-30 day period after vaccination among children receiving 786,725 doses of RotaTeq, including 309,844 first doses. There was no statistically significant increased risk of intussusception after any dose or after the first dose in either the 1-7 day or 1-30 day period after vaccination. This large-

scale study had 80% power to detect a relative risk of 6.4 or greater in the 1-7-day period after dose 1.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

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.
For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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 P1A[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 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, 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 (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 protection against non-vaccine G-serotypes that may contain P1A[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 3. 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 5).

Table 3
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 the rate of hospitalisations, emergency department visits, non-urgent care visits, and parent/legal guardian work loss days. The reduction in hospitalisations 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 (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. RotaTeq reduced health care contacts through the prevention of hospitalisations, emergency department visits and non-urgent visits for rotavirus gastroenteritis as shown in Tables 4 and 5.

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

Type of Health Care Contact	RotaTeq	Placebo	% Rate Reduction and 95% CI
Combined Endpoint (Hospitalisations and Emergency Department Visits)*	28	493	94.4 (91.6, 96.2)
Hospitalisations	13	226	94.3 (89.9, 97.0)
Emergency Department Visits	15	267	94.4 (90.5, 96.9)
Non-Urgent Visits**	13	98	86.0 (73.9, 92.5)

*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 hospitalisations or emergency department visits for rotavirus gastroenteritis in year 3.
**N=5,673 infants vaccinated, follow-up for up to 2 years in REST.

Table 5
Number of Hospitalisations and Emergency Department (ED) Visits for Rotavirus Gastroenteritis According to the G Serotype Identified in the Subject's Stool for up to 2 years after vaccination in REST and for up to 3 years post-vaccination in the Extension Study**

Serotype	Number of Hospitalisations and/or ED Visits for Rotavirus Gastroenteritis		% Rate Reduction (95% CI)
	RotaTeq (N=34,035)	Placebo (N=34,003)	
G1	20	440	95.5 (92.8, 97.2)*
G2	2	11	81.9 (16.1, 98.0)*
G3	2	18	89.0 (53.3, 98.7)*
G4	4	24	83.4 (51.2, 95.8)*
G9	1	17	94.2 (62.2, 99.9)*

* Statistically significant
** There were no typeable episodes of rotavirus gastroenteritis leading to hospitalisations or emergency department visits for rotavirus gastroenteritis in year 3.

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 RotaTeq compared with 487 work loss days among parents/guardians of placebo recipients.

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 hospitalisations 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 hospitalisations 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 in REST

	RotaTeq	Placebo	% Rate Reduction and (95% CI)
	Number of cases / evaluable subjects	Number of cases / evaluable subjects	
From ≥14 days after dose 1 until dose 2	0 / 29,417	15 / 29,434	100 (72.2, 100)
From ≥14 days after dose 2 until dose 3	2 / 29,496	22 / 29,565	90.9 (62.9, 99.0)

The complete 3-dose vaccination series should be administered to provide the level and duration of protection observed in the clinical studies (see Section 4.4 Special Warnings and Precautions for Use).

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 7).

Table 7
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. In a subset of 204 vaccinated infants (99 in the vaccine group), protective efficacy was 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 (see Table 8).

Table 8
Efficacy of RotaTeq in pre-term infants

Reduction in incidence of rotavirus gastroenteritis of any severity 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 (95 % CI)
	RotaTeq	Placebo	
Rotavirus Gastroenteritis Cases	3/75	10/78	70.3 (<0, 94.7)

In 2,070 vaccinated infants (1,007 in the vaccine group), protective efficacy was also measured by a reduction in the rate of hospitalisations and emergency department visits for rotavirus gastroenteritis caused by vaccine serotypes (G1-G4) from 14 days for up to 2 years after the third dose (see Table 9).

Table 9
Efficacy of RotaTeq in pre-term infants

Reduction in hospitalisations and emergency department visits for rotavirus gastroenteritis caused by the G-serotypes included in the vaccine for up to 2 years post-vaccination in REST

	(Number of visits / Number of evaluable subjects)		% Efficacy (95% CI)
	RotaTeq	Placebo	
Hospitalisations and emergency visits	0/764	15/817	100 (74,100)

Likewise, the protective efficacy, as measured by a reduction in the rate of hospitalisations 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 10 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 10
Post-Marketing Studies Demonstrating the Effectiveness of RotaTeq to Prevent Gastroenteritis

Study design (Region)	Study population	Endpoints	Effectiveness % [95%CI]	RV seasons
Claims database analysis (US)*	33,140 vaccinated 26,167 unvaccinated Aged ≥7 months Received 3 doses	Hospitalization and Emergency Department (ED) visits due to RVGE†	100% [87,100]	2007-2008
		Outpatient visits due to RVGE	96% [76,100]	
		Hospitalization and ED visits due to all-cause gastroenteritis	59% [47,68]	
		Outpatient visits due to all-cause gastroenteritis	28% [22, 33]	
Cohort study (France)‡	1,895 vaccinated with 3 doses 2,102 unvaccinated Aged <2 years	Hospitalization 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	80% [74,84]	2011-2012 2012-2013
		Strain-specific		
		- G1P[8]	89% [55,97]	
		- G2P[4]	87% [65,95]	
		- G3P[8]	80% [64,89]	
		- G12P[8]	78% [71,84]	
		Age-specific		
		- 1st year of life	91% [78,96]	
		- 2nd year of life	82% [69,89]	
		- 3rd year of life	88% [78,93]	
		- 4th year of life	76% [51,88]	
		- 5th year of life	60% [16,81]	
		- 6th-7th year of life	69% [43,84]	

*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

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 11). The immune responses to the specified vaccines were unaffected by RotaTeq.

Table 11
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 human serotypes G1, G2, G3, G4 and P1A[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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Not applicable

Distribution

Not applicable

Metabolism

Not applicable

Excretion

Not applicable

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

RotaTeq has not been evaluated for its mutagenic potential.

Carcinogenicity

RotaTeq has not been evaluated for its carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

sucrose
sodium citrate dihydrate
monobasic sodium phosphate monohydrate
sodium hydroxide

polysorbate 80
Rotavirus diluent
Low Protein Kidney Medium-3

There are no preservatives or thiomersal present.

6.2 INCOMPATIBILITIES

Please refer to 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS for further information.

6.3 SHELF LIFE

The expiry date can be found on the packaging. In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

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 CONTENTS OF CONTAINER

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.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Not applicable

CAS number

Not applicable

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A, 26 Talavera Road
Macquarie Park NSW 2113
www.msd-australia.com.au

Name and address of distributor

Seqirus (Australia) Pty Ltd
63 Poplar Road
Parkville
Victoria 3052
Australia

9 DATE OF FIRST APPROVAL

21 February 2011

10 DATE OF REVISION

27 March 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformatting of PI according to TGA Product Information form (April 2018)
4.9	Addition of text to reflect post-marketing reports of overdosage