HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ROTARIX safely and effectively. See full prescribing information for ROTARIX.

ROTARIX (Rotavirus Vaccine, Live, Oral)
Oral Suspension
Initial U.S. Approval: 2008

----------INDICATIONS AND USAGE----------

ROTARIX is a vaccine indicated for the prevention of rotavirus gastroenteritis caused by G1 and non-G1 types (G3, G4, and G9). ROTARIX is approved for use in infants 6 weeks to 24 weeks of age. (1)

---------- DOSAGE AND ADMINISTRATION ----------

FOR ORAL USE ONLY. (2.1)

- Each dose is 1 mL administered orally. (2.2)
- Administer first dose to infants beginning at 6 weeks of age. (2.2)
- Administer second dose after an interval of at least 4 weeks and prior to 24 weeks of age. (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------

- Vial of lyophilized vaccine to be reconstituted with a liquid diluent in a prefilled oral applicator. (3)
- Each 1-mL dose contains a suspension of at least $10^{6.0}$ median Cell Culture Infective Dose ($CCID_{50}$) of live, attenuated human G1P[8] rotavirus after reconstitution. (3)

----------CONTRAINDICATIONS----------

- A demonstrated history of hypersensitivity to the vaccine or any component of the vaccine. (4.1, 11)
- History of uncorrected congenital malformation of the gastrointestinal tract that would predispose the infant to intussusception. (4.2)
- History of intussusception. (4.3)
- History of Severe Combined Immunodeficiency Disease (SCID). (4.4, 6.2)

----------WARNINGS AND PRECAUTIONS ----------

- The tip caps of the prefilled oral applicators of diluent contain natural rubber latex which may cause allergic reactions. (5.1)
- Administration of ROTARIX in infants suffering from acute diarrhea or vomiting should be delayed. Safety and effectiveness of ROTARIX in infants with chronic gastrointestinal disorders have not been evaluated. (5.2)
- Safety and effectiveness of ROTARIX in infants with known primary or secondary immunodeficiencies have not been established. (5.3)
- In a postmarketing study, cases of intussusception were observed in temporal association within 31 days following the first dose of ROTARIX, with a clustering of cases in the first 7 days. (5.5, 6.2)

----------ADVERSE REACTIONS ----------

Common (≥5%) solicited adverse events included fussiness/irritability, cough/runny nose, fever, loss of appetite, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: xx/xxxx

FULL PRESCRIBING INFORMATION: CONTENTS*

*****Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ROTARIX® is indicated for the prevention of rotavirus gastroenteritis caused by G1 and non-G1 types (G3, G4, and G9) when administered as a 2-dose series *[see Clinical Studies (14.3)]*. ROTARIX is approved for use in infants 6 weeks to 24 weeks of age.

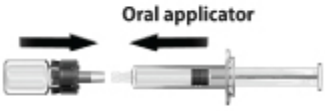
2 DOSAGE AND ADMINISTRATION

2.1 Reconstitution Instructions for Oral Administration

For oral use only. Not for injection.

Reconstitute only with accompanying diluent. Do not mix ROTARIX with other vaccines or solutions.

Remove vial cap and push transfer adapter onto vial (lyophilized vaccine).



Shake diluent in oral applicator (white, turbid suspension). Connect oral applicator to transfer adapter.

Push plunger of oral applicator to transfer diluent into vial. Suspension will appear white and turbid.

Withdraw vaccine into oral applicator.

Twist and remove the oral applicator.

Ready for **oral** administration.

Do not use a needle with ROTARIX.
Not for injection.

2.2 Recommended Dose and Schedule

The vaccination series consists of two 1-mL doses administered **orally**. The first dose should be administered to infants beginning at 6 weeks of age. There should be an interval of at least 4 weeks between the first and second dose. The 2-dose series should be completed by 24 weeks of age.

Safety and effectiveness have not been evaluated if ROTARIX were administered for the first dose and another rotavirus vaccine were administered for the second dose or vice versa.

In the event that the infant spits out or regurgitates most of the vaccine dose, a single replacement dose may be considered at the same vaccination visit.

2.3 Infant Feeding

Breastfeeding was permitted in clinical studies. There was no evidence to suggest that breastfeeding reduced the protection against rotavirus gastroenteritis afforded by ROTARIX.

There are no restrictions on the infant's liquid consumption, including breast milk, either before or after vaccination with ROTARIX.

3 DOSAGE FORMS AND STRENGTHS

ROTARIX is available as a vial of lyophilized vaccine to be reconstituted with a liquid diluent in a prefilled oral applicator.

Each 1-mL dose contains a suspension of at least $10^{6.0}$ median Cell Culture Infective Dose ($CCID_{50}$) of live, attenuated human G1P[8] rotavirus after reconstitution.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

A demonstrated history of hypersensitivity to any component of the vaccine.

Infants who develop symptoms suggestive of hypersensitivity after receiving a dose of ROTARIX should not receive further doses of ROTARIX.

4.2 Gastrointestinal Tract Congenital Malformation

Infants with a history of uncorrected congenital malformation of the gastrointestinal tract (such as Meckel's diverticulum) that would predispose the infant for intussusception should not receive ROTARIX.

4.3 History of Intussusception

Infants with a history of intussusception should not receive ROTARIX *[see Warnings and Precautions (5.5)]*. In postmarketing experience, intussusception resulting in death following a second dose has been reported following a history of intussusception after the first dose *[see Adverse Reactions (6.2)]*.

4.4 Severe Combined Immunodeficiency Disease

Infants with Severe Combined Immunodeficiency Disease (SCID) should not receive ROTARIX. Postmarketing reports of gastroenteritis, including severe diarrhea and prolonged shedding of vaccine virus, have been reported in infants who were administered live, oral rotavirus vaccines and later identified as having SCID *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Latex

The tip caps of the prefilled oral applicators of diluent contain natural rubber latex which may cause allergic reactions.

5.2 Gastrointestinal Disorders

Administration of ROTARIX should be delayed in infants suffering from acute diarrhea or vomiting.

Safety and effectiveness of ROTARIX in infants with chronic gastrointestinal disorders have not been evaluated. *[See Contraindications (4.2).]*

5.3 Altered Immunocompetence

Safety and effectiveness of ROTARIX in infants with known primary or secondary immunodeficiencies, including infants with human immunodeficiency virus (HIV), infants on immunosuppressive therapy, or infants with malignant neoplasms affecting the bone marrow or lymphatic system have not been established.

5.4 Shedding and Transmission

Rotavirus shedding in stool occurs after vaccination with peak excretion occurring around Day 7 after Dose 1.

One clinical trial demonstrated that vaccinees transmit vaccine virus to healthy seronegative contacts *[see Clinical Pharmacology (12.2)]*.

The potential for transmission of vaccine virus following vaccination should be weighed against the possibility of acquiring and transmitting natural rotavirus. Caution is advised when considering whether to administer ROTARIX to individuals with immunodeficient close contacts, such as individuals with malignancies, primary immunodeficiency, or receiving immunosuppressive therapy.

5.5 Intussusception

Following administration of a previously licensed oral live rhesus rotavirus-based vaccine, an increased risk of intussusception was observed.[1] The risk of intussusception with ROTARIX was evaluated in a pre-licensure randomized, placebo-controlled safety study (including 63,225 infants) conducted in Latin America and Finland. No increased risk of intussusception was observed in this clinical trial following administration of ROTARIX when compared with placebo. *[See Adverse Reactions (6.1).]*

In a postmarketing, observational study conducted in Mexico, cases of intussusception were observed in temporal association within 31 days following the first dose of ROTARIX, with a clustering of cases in the first 7 days. *[See Adverse Reactions (6.2).]*

Other postmarketing observational studies conducted in Brazil and Australia also suggest an increased risk of intussusception within the first 7 days following the second dose of ROTARIX.[2,3] *[See Adverse Reactions (6.2).]*

In worldwide passive postmarketing surveillance, cases of intussusception have been reported in temporal association with ROTARIX *[see Adverse Reactions (6.2)]*.

5.6 Post-exposure Prophylaxis

Safety and effectiveness of ROTARIX when administered after exposure to rotavirus have not been evaluated.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine, and may not reflect the rates observed in practice. As with any vaccine, there is the possibility that broad use of ROTARIX could reveal adverse reactions not observed in clinical trials.

Solicited and unsolicited adverse events, serious adverse events and cases of intussusception were collected in 7 clinical studies. Cases of intussusception and serious adverse events were collected in an additional large safety study. These 8 clinical studies evaluated a total of 71,209 infants who received ROTARIX (N = 36,755) or placebo (N = 34,454). The racial distribution for these studies was as follows: Hispanic 73.4%, white 16.2%, black 1.0%, and other 9.4%; 51% were male.

Solicited Adverse Events

In 7 clinical studies, detailed safety information was collected by parents/guardians for 8 consecutive days following vaccination with ROTARIX (i.e., day of vaccination and the next 7 days). A diary card was completed to record fussiness/irritability, cough/runny nose, the infant's temperature, loss of appetite, vomiting, or diarrhea on a daily basis during the first week following each dose of ROTARIX or placebo. Adverse events among recipients of ROTARIX and placebo occurred at similar rates (Table 1).

Table 1. Solicited Adverse Events within 8 Days Following Doses 1 and 2 of ROTARIX or Placebo (Total Vaccinated Cohort)

	Dose 1		Dose 2	
	ROTARIX N = 3,284 %	**Placebo N = 2,013 %**	**ROTARIX N = 3,201 %**	**Placebo N = 1,973 %**
Fussiness/irritability[a]	52	52	42	42
Cough/runny nose[b]	28	30	31	33
Fever[c]	25	33	28	34
Loss of appetite[d]	25	25	21	21
Vomiting	13	11	8	8
Diarrhea	4	3	3	3

Total vaccinated cohort = All vaccinated infants for whom safety data were available.
N = Number of infants for whom at least one symptom sheet was completed.
[a] Defined as crying more than usual.
[b] Data not collected in 1 of 7 studies; Dose 1: ROTARIX N = 2,583; placebo N = 1,897; Dose 2: ROTARIX N = 2,522; placebo N = 1,863.
[c] Defined as temperature ≥100.4°F (≥38.0°C) rectally or ≥99.5°F (≥37.5°C) orally.
[d] Defined as eating less than usual.

Unsolicited Adverse Events

Infants were monitored for unsolicited serious and non-serious adverse events that occurred in the 31-day period following vaccination in 7 clinical studies. The following adverse events occurred at a statistically higher incidence (95% Confidence Interval [CI] of Relative Risk excluding 1) among recipients of ROTARIX (N = 5,082) as compared with placebo recipients (N = 2,902): irritability (ROTARIX 11.4%, placebo 8.7%) and flatulence (ROTARIX 2.2%, placebo 1.3%).

Serious Adverse Events (SAEs)

Infants were monitored for serious adverse events that occurred in the 31-day period following vaccination in 8 clinical studies. Serious adverse events occurred in 1.7% of recipients of ROTARIX (N = 36,755) as compared with 1.9% of placebo recipients (N = 34,454). Among placebo recipients, diarrhea (placebo 0.07%, ROTARIX 0.02%), dehydration (placebo 0.06%, ROTARIX 0.02%), and gastroenteritis (placebo 0.3%, ROTARIX 0.2%) occurred at a statistically higher incidence (95% CI of Relative Risk excluding 1) as compared with recipients of ROTARIX.

Deaths

During the entire course of 8 clinical studies, there were 68 (0.19%) deaths following administration of ROTARIX (N = 36,755) and 50 (0.15%) deaths following placebo

administration (N = 34,454). The most commonly reported cause of death following vaccination was pneumonia, which was observed in 19 (0.05%) recipients of ROTARIX and 10 (0.03%) placebo recipients (Relative Risk: 1.74, 95% CI: 0.76, 4.23).

Intussusception

In a controlled safety study conducted in Latin America and Finland, the risk of intussusception was evaluated in 63,225 infants (31,673 received ROTARIX and 31,552 received placebo). Infants were monitored by active surveillance including independent, complementary methods (prospective hospital surveillance and parent reporting at scheduled study visits) to identify potential cases of intussusception within 31 days after vaccination and, in a subset of 20,169 infants (10,159 received ROTARIX and 10,010 received placebo), up to one year after the first dose.

No increased risk of intussusception following administration of ROTARIX was observed within a 31-day period following any dose, and rates were comparable to the placebo group after a median of 100 days (Table 2). In a subset of 20,169 infants (10,159 received ROTARIX and 10,010 received placebo) followed up to one year after Dose 1, there were 4 cases of intussusception with ROTARIX compared with 14 cases of intussusception with placebo (Relative Risk: 0.28 [95% CI: 0.10, 0.81]). All of the infants who developed intussusception recovered without sequelae.

Table 2. Intussusception and Relative Risk with ROTARIX Compared with Placebo

Confirmed Cases of Intussusception	**ROTARIX N = 31,673**	**Placebo N = 31,552**
Within 31 days following diagnosis after any dose	6	7
Relative Risk (95% CI)	0.85 (0.30, 2.42)	
Within 100 days following Dose 1[a]	9	16
Relative Risk (95% CI)	0.56 (0.25, 1.24)	

CI = Confidence Interval.

[a] Median duration after Dose 1 (follow-up visit at 30 to 90 days after Dose 2).

Among vaccine recipients, there were no confirmed cases of intussusception within the 0- to 14-day period after the first dose (Table 3), which was the period of highest risk for the previously licensed oral live rhesus rotavirus-based vaccine.[1]

Table 3. Intussusception Cases by Day Range in Relation to Dose

	Dose 1		Dose 2		Any Dose	
Day Range	**ROTARIX N = 31,673**	**Placebo N = 31,552**	**ROTARIX N = 29,616**	**Placebo N = 29,465**	**ROTARIX N = 31,673**	**Placebo N = 31,552**
0-7	0	0	2	0	2	0
8-14	0	0	0	2	0	2
15-21	1	1	2	1	3	2
22-30	0	1	1	2	1	3
Total (0-30)	1	2	5	5	6	7

Kawasaki Disease

Kawasaki disease has been reported in 18 (0.035%) recipients of ROTARIX and 9 (0.021%) placebo recipients from 16 completed or ongoing clinical trials. Of the 27 cases, 5 occurred following ROTARIX in clinical trials that were either not placebo-controlled or 1:1 randomized. In placebo-controlled trials, Kawasaki disease was reported in 17 recipients of ROTARIX and 9 placebo recipients (Relative Risk: 1.71 [95% CI: 0.71, 4.38]). Three of the 27 cases were reported within 30 days post-vaccination: 2 cases (ROTARIX = 1, placebo = 1) were from placebo-controlled trials (Relative Risk: 1.00 [95% CI: 0.01, 78.35]) and one case following ROTARIX was from a non–placebo-controlled trial. Among recipients of ROTARIX, the time of onset after study dose ranged 3 days to 19 months.

6.2 Postmarketing Experience

The temporal association between vaccination with ROTARIX and intussusception was evaluated in a hospital-based active surveillance study that identified infants with intussusception at participating hospitals in Mexico. Using a self-controlled case series method,[4] the incidence of intussusception during the first 7 days after receipt of ROTARIX and during the 31-day period after receipt of ROTARIX was compared with a control period. The control period was from birth to one year, excluding the pre-defined risk period (first 7 days or first 31 days post-vaccination, respectively).

Over a 2-year period, the participating hospitals provided health services to approximately 1 million infants under 1 year of age. Among 750 infants with intussusception, the relative incidence of intussusception in the 31-day period after the first dose of ROTARIX compared with the control period was 1.96 (95.5% CI: 1.46, 2.63)]; the relative incidence of intussusception in the first 7 days after the first dose of ROTARIX compared with the control period was 6.07 (95.5% CI: 4.20, 8.63).

The Mexico study did not take into account all medical conditions that may predispose infants to intussusception. The results may not be generalizable to US infants who have a lower background rate of intussusception than Mexican infants. However, if a temporal increase in the risk for intussusception following ROTARIX similar in magnitude to that observed in the

Mexico study does exist in US infants, it is estimated that approximately 1 to 3 additional cases of intussusception hospitalizations would occur per 100,000 vaccinated infants in the US within 7 days following the first dose of ROTARIX. In the first year of life, the background rate of intussusception hospitalizations in the US has been estimated to be approximately 34 per 100,000 infants.[5]

Other postmarketing observational studies conducted in Brazil and Australia also suggest an increased risk of intussusception within the first 7 days following the second dose of ROTARIX.[2,3]

Worldwide passive postmarketing surveillance data suggest that most cases of intussusception reported following ROTARIX occur in the 7-day period after the first dose.

The following adverse events have been reported since market introduction of ROTARIX. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccination with ROTARIX.

Gastrointestinal Disorders

Intussusception (including death), recurrent intussusception (including death), hematochezia, gastroenteritis with vaccine viral shedding in infants with SCID.

Blood and Lymphatic System Disorders

Idiopathic thrombocytopenic purpura.

Vascular Disorders

Kawasaki disease.

General Disorders and Administration Site Conditions

Maladministration.

7 DRUG INTERACTIONS

7.1 Concomitant Vaccine Administration

In clinical trials, ROTARIX was administered concomitantly with US-licensed and non–US-licensed vaccines. In a US coadministration study in 484 infants, there was no evidence of interference in the immune responses to any of the antigens when PEDIARIX® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine], a US-licensed 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.), and a US-licensed Hib conjugate vaccine (Sanofi Pasteur SA) were coadministered with ROTARIX as compared with separate administration of ROTARIX.

7.2 Immunosuppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to ROTARIX. *[See Warnings and Precautions (5.3).]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with ROTARIX. It is also not known whether ROTARIX can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

8.4 Pediatric Use

Safety and effectiveness of ROTARIX in infants younger than 6 weeks or older than 24 weeks of age have not been evaluated.

The effectiveness of ROTARIX in pre-term infants has not been established. Safety data are available in pre-term infants (ROTARIX = 134, placebo = 120) with a reported gestational age ≤36 weeks. These pre-term infants were followed for serious adverse events up to 30 to 90 days after Dose 2. Serious adverse events were observed in 5.2% of recipients of ROTARIX as compared with 5.0% of placebo recipients. No deaths or cases of intussusception were reported in this population.

11 DESCRIPTION

ROTARIX (Rotavirus Vaccine, Live, Oral), for oral administration, is a live, attenuated rotavirus vaccine derived from the human 89-12 strain which belongs to G1P[8] type. The rotavirus strain is propagated on Vero cells. After reconstitution, the final formulation (1 mL) contains at least $10^{6.0}$ median Cell Culture Infective Dose ($CCID_{50}$) of live, attenuated rotavirus.

The lyophilized vaccine contains amino acids, dextran, Dulbecco's Modified Eagle Medium (DMEM), sorbitol, and sucrose. DMEM contains the following ingredients: sodium chloride, potassium chloride, magnesium sulfate, ferric (III) nitrate, sodium phosphate, sodium pyruvate, D-glucose, concentrated vitamin solution, L-cystine, L-tyrosine, amino acids solution, L-glutamine, calcium chloride, sodium hydrogenocarbonate, and phenol red.

In the manufacturing process, porcine-derived materials are used. Porcine circovirus type 1 (PCV-1) is present in ROTARIX. PCV-1 is not known to cause disease in humans.

The liquid diluent contains calcium carbonate, sterile water, and xanthan. The diluent includes an antacid component (calcium carbonate) to protect the vaccine during passage through the stomach and prevent its inactivation due to the acidic environment of the stomach.

ROTARIX is available in single-dose vials of lyophilized vaccine, accompanied by a prefilled oral applicator of liquid diluent *[see How Supplied/Storage and Handling (16)]*. The tip caps of the prefilled oral applicators contain natural rubber latex; the vial stoppers are not made with natural rubber latex.

ROTARIX contains no preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Prior to rotavirus vaccination programs, rotavirus infected nearly all children by the time they were 5 years of age. Severe, dehydrating rotavirus gastroenteritis occurs primarily among children aged 3 to 35 months.[6] Among children up to 3 years of age, approximately 16% of cases before 6 months of age result in hospitalization.[7]

The exact immunologic mechanism by which ROTARIX protects against rotavirus gastroenteritis is unknown *[see Clinical Pharmacology (12.2)]*. ROTARIX contains a live, attenuated human rotavirus that replicates in the small intestine and induces immunity.

12.2 Pharmacodynamics

Immunogenicity

A relationship between antibody responses to rotavirus vaccination and protection against rotavirus gastroenteritis has not been established. Seroconversion was defined as the appearance of anti-rotavirus IgA antibodies (concentration ≥20 U/mL) post-vaccination in the serum of infants previously negative for rotavirus. In 2 safety and efficacy studies, one to two months after a 2-dose series, 86.5% of 787 recipients of ROTARIX seroconverted compared with 6.7% of 420 placebo recipients and 76.8% of 393 recipients of ROTARIX seroconverted compared with 9.7% of 341 placebo recipients, respectively.

Shedding and Transmission

A prospective, randomized, double-blind, placebo-controlled study was performed in the Dominican Republic in twins within the same household to assess whether transmission of vaccine virus occurs from a vaccinated infant to a non-vaccinated infant. One hundred pairs of healthy twins 6 to 14 weeks of age (gestational age ≥32 weeks) were randomized with one twin to receive ROTARIX (N = 100) and the other twin to receive placebo (N = 100). Twenty subjects in each arm were excluded for reasons such as having rotavirus antibody at baseline. Stool samples were collected on the day of or 1 day prior to each dose, as well as 3 times weekly for 6 consecutive weeks after each dose of ROTARIX or placebo. Transmission was defined as presence of the vaccine virus strain in any stool sample from a twin receiving placebo.

Transmitted vaccine virus was identified in 15 of 80 twins receiving placebo (18.8% [95% CI: 10.9, 29.0]). Median duration of the rotavirus shedding was 10 days in twins who received ROTARIX as compared with 4 days in twins who received placebo in whom the vaccine virus

was transmitted. In the 15 twins who received placebo, no gastrointestinal symptoms related to transmitted vaccine virus were observed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ROTARIX has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

14 CLINICAL STUDIES

14.1 Efficacy Studies

The data demonstrating the efficacy of ROTARIX in preventing rotavirus gastroenteritis come from 24,163 infants randomized in two placebo-controlled studies conducted in 17 countries in Europe and Latin America. In these studies, oral polio vaccine (OPV) was not coadministered; however, other routine childhood vaccines could be concomitantly administered. Breastfeeding was permitted in both studies.

A randomized, double-blind, placebo-controlled study was conducted in 6 European countries. A total of 3,994 infants were enrolled to receive ROTARIX (n = 2,646) or placebo (n = 1,348). Vaccine or placebo was given to healthy infants as a 2-dose series with the first dose administered orally from 6 through 14 weeks of age followed by one additional dose administered at least 4 weeks after the first dose. The 2-dose series was completed by 24 weeks of age. For both vaccination groups, 98.3% of infants were white and 53% were male.

The clinical case definition of rotavirus gastroenteritis was an episode of diarrhea (passage of 3 or more loose or watery stools within a day), with or without vomiting, where rotavirus was identified in a stool sample. Severity of gastroenteritis was determined by a clinical scoring system, the Vesikari scale, assessing the duration and intensity of diarrhea and vomiting, the intensity of fever, use of rehydration therapy, or hospitalization for each episode. Scores range from 0 to 20, where higher scores indicate greater severity. An episode of gastroenteritis with a score of 11 or greater was considered severe.[8]

The primary efficacy endpoint was prevention of any grade of severity of rotavirus gastroenteritis caused by naturally occurring rotavirus from 2 weeks after the second dose through one rotavirus season (according to protocol, ATP). Other efficacy evaluations included prevention of severe rotavirus gastroenteritis, as defined by the Vesikari scale, and reductions in hospitalizations due to rotavirus gastroenteritis and all-cause gastroenteritis regardless of presumed etiology. Analyses were also done to evaluate the efficacy of ROTARIX against rotavirus gastroenteritis among infants who received at least one vaccination (total vaccinated cohort, TVC).

Efficacy of ROTARIX against any grade of severity of rotavirus gastroenteritis through one rotavirus season was 87.1% (95% CI: 79.6, 92.1); TVC efficacy was 87.3% (95% CI: 80.3,

92.0). Efficacy against severe rotavirus gastroenteritis through one rotavirus season was 95.8% (95% CI: 89.6, 98.7); TVC efficacy was 96.0% (95% CI: 90.2, 98.8) (Table 4). The protective effect of ROTARIX against any grade of severity of rotavirus gastroenteritis observed immediately following Dose 1 administration and prior to Dose 2 was 89.8% (95% CI: 8.9, 99.8).

Efficacy of ROTARIX in reducing hospitalizations for rotavirus gastroenteritis through one rotavirus season was 100% (95% CI: 81.8, 100); TVC efficacy was 100% (95% CI: 81.7, 100) (Table 4). ROTARIX reduced hospitalizations for all-cause gastroenteritis regardless of presumed etiology by 74.7% (95% CI: 45.5, 88.9).

Table 4. Efficacy Evaluation of ROTARIX through One Rotavirus Season

	According to Protocol[a]		**Total Vaccinated Cohort[b]**	
Infants in Cohort	**ROTARIX N = 2,572**	**Placebo N = 1,302**	**ROTARIX N = 2,646**	**Placebo N = 1,348**
Gastroenteritis cases				
Any severity	24	94	26	104
Severe[c]	5	60	5	64
Efficacy estimate against RV GE				
Any severity	87.1%[d]		87.3%[d]	
(95% CI)	(79.6, 92.1)		(80.3, 92.0)	
Severe[c]	95.8%[d]		96.0%[d]	
(95% CI)	(89.6, 98.7)		(90.2, 98.8)	
Cases of hospitalization due to RV GE	0	12	0	12
Efficacy in reducing hospitalizations due to RV GE	100%[d]		100%[d]	
(95% CI)	(81.8, 100)		(81.7, 100)	

RV GE = Rotavirus gastroenteritis; CI = Confidence Interval.

[a] ATP analysis includes all infants in the efficacy cohort who received two doses of vaccine according to randomization.

[b] TVC analysis includes all infants in the efficacy cohort who received at least one dose of vaccine or placebo.

[c] Severe gastroenteritis defined as ≥11 on the Vesikari scale.

[d] Statistically significant versus placebo (P <0.001).

A randomized, double-blind, placebo-controlled study was conducted in 11 countries in Latin America and Finland. A total of 63,225 infants received ROTARIX (n = 31,673) or placebo (n = 31,552). An efficacy subset of these infants consisting of 20,169 infants from Latin America received ROTARIX (n = 10,159) or placebo (n = 10,010). Vaccine or placebo was given to healthy infants as a 2-dose series with the first dose administered orally from 6 through 13 weeks

of age followed by one additional dose administered at least 4 weeks after the first dose. The 2-dose series was completed by 24 weeks of age. For both vaccination groups, the racial distribution of the efficacy subset was as follows: Hispanic 85.8%, white 7.9%, black 1.1%, and other 5.2%; 51% were male.

The clinical case definition of severe rotavirus gastroenteritis was an episode of diarrhea (passage of 3 or more loose or watery stools within a day), with or without vomiting, where rotavirus was identified in a stool sample, requiring hospitalization and/or rehydration therapy equivalent to World Health Organization (WHO) plan B (oral rehydration therapy) or plan C (intravenous rehydration therapy) in a medical facility.

The primary efficacy endpoint was prevention of severe rotavirus gastroenteritis caused by naturally occurring rotavirus from 2 weeks after the second dose through one year (ATP). Analyses were done to evaluate the efficacy of ROTARIX against severe rotavirus gastroenteritis among infants who received at least one vaccination (TVC). Reduction in hospitalizations due to rotavirus gastroenteritis was also evaluated (ATP).

Efficacy of ROTARIX against severe rotavirus gastroenteritis through one year was 84.7% (95% CI: 71.7, 92.4); TVC efficacy was 81.1% (95% CI: 68.5, 89.3) (Table 5).

Efficacy of ROTARIX in reducing hospitalizations for rotavirus gastroenteritis through one year was 85.0% (95% CI: 69.6, 93.5); TVC efficacy was 80.8% (95% CI: 65.7, 90.0) (Table 5).

Table 5. Efficacy Evaluation of ROTARIX through One Year

	According to Protocol[a]		**Total Vaccinated Cohort[b]**	
Infants in Cohort	**ROTARIX N = 9,009**	**Placebo N = 8,858**	**ROTARIX N = 10,159**	**Placebo N = 10,010**
Gastroenteritis cases				
Severe	12	77	18	94
Efficacy estimate against RV GE				
Severe	84.7%[c]		81.1%[c]	
(95% CI)	(71.7, 92.4)		(68.5, 89.3)	
Cases of hospitalization due to RV GE	9	59	14	72
Efficacy in reducing hospitalizations due to RV GE	85.0%[c]		80.8%[c]	
(95% CI)	(69.6, 93.5)		(65.7, 90.0)	

RV GE = Rotavirus gastroenteritis; CI = Confidence Interval.

[a] ATP analysis includes all infants in the efficacy cohort who received two doses of vaccine according to randomization.

[b] TVC analysis includes all infants in the efficacy cohort who received at least one dose of vaccine or placebo.

[c] Statistically significant versus placebo (P <0.001).

14.2 Efficacy through Two Rotavirus Seasons

The efficacy of ROTARIX persisting through two rotavirus seasons was evaluated in two studies.

In the European study, the efficacy of ROTARIX against any grade of severity of rotavirus gastroenteritis through two rotavirus seasons was 78.9% (95% CI: 72.7, 83.8). Efficacy in preventing any grade of severity of rotavirus gastroenteritis cases occurring only during the second season post-vaccination was 71.9% (95% CI: 61.2, 79.8). The efficacy of ROTARIX against severe rotavirus gastroenteritis through two rotavirus seasons was 90.4% (95% CI: 85.1, 94.1). Efficacy in preventing severe rotavirus gastroenteritis cases occurring only during the second season post-vaccination was 85.6% (95% CI: 75.8, 91.9).

The efficacy of ROTARIX in reducing hospitalizations for rotavirus gastroenteritis through two rotavirus seasons was 96.0% (95% CI: 83.8, 99.5).

In the Latin American study, the efficacy of ROTARIX against severe rotavirus gastroenteritis through two years was 80.5% (95% CI: 71.3, 87.1). Efficacy in preventing severe rotavirus gastroenteritis cases occurring only during the second year post-vaccination was 79.0% (95% CI: 66.4, 87.4). The efficacy of ROTARIX in reducing hospitalizations for rotavirus gastroenteritis through two years was 83.0% (95% CI: 73.1, 89.7).

The efficacy of ROTARIX beyond the second season post-vaccination was not evaluated.

14.3 Efficacy against Specific Rotavirus Types

The type-specific efficacy against any grade of severity and severe rotavirus gastroenteritis caused by G1P[8], G3P[8], G4P[8], G9P[8], and combined non-G1 (G2, G3, G4, G9) types was statistically significant through one year. Additionally, type-specific efficacy against any grade of severity and severe rotavirus gastroenteritis caused by G1P[8], G2P[4], G3P[8], G4P[8], G9P[8], and combined non-G1 (G2, G3, G4, G9) types was statistically significant through two years (Table 6).

Table 6. Type-Specific Efficacy of ROTARIX against Any Grade of Severity and Severe Rotavirus Gastroenteritis (According to Protocol)

	Through One Rotavirus Season			Through Two Rotavirus Seasons		
	Number of Cases			Number of Cases		
Type Identified[a]	ROTARIX N = 2,572	Placebo N = 1,302	% Efficacy (95% CI)	ROTARIX N = 2,572	Placebo N = 1,302	% Efficacy (95% CI)
ANY GRADE OF SEVERITY						
G1P[8]	4	46	95.6%[b] (87.9, 98.8)	18	89[c,d]	89.8%[b] (82.9, 94.2)
G2P[4]	3	4[c]	NS	14	17[c]	58.3%[b] (10.1, 81.0)
G3P[8]	1	5	89.9%[b] (9.5, 99.8)	3	10	84.8%[b] (41.0, 97.3)
G4P[8]	3	13	88.3%[b] (57.5, 97.9)	6	18	83.1%[b] (55.6, 94.5)
G9P[8]	13	27	75.6%[b] (51.1, 88.5)	38	71[d]	72.9%[b] (59.3, 82.2)
Combined non-G1 (G2, G3, G4, G9, G12) types[e]	20	49	79.3%[b] (64.6, 88.4)	62	116	72.9%[b] (62.9, 80.5)
SEVERE						
G1P[8]	2	28	96.4%[b] (85.7, 99.6)	4	57	96.4%[b] (90.4, 99.1)
G2P[4]	1	2[c]	NS	2	7[c]	85.5%[b] (24.0, 98.5)
G3P[8]	0	5	100%[b] (44.8, 100)	1	8	93.7%[b] (52.8, 99.9)
G4P[8]	0	7	100%[b] (64.9, 100)	1	11	95.4%[b] (68.3, 99.9)
G9P[8]	2	19	94.7%[b] (77.9, 99.4)	13	44[d]	85.0%[b] (71.7, 92.6)
Combined non-G1 (G2, G3, G4, G9, G12) types[e]	3	33	95.4%[b] (85.3, 99.1)	17	70	87.7%[b] (78.9, 93.2)

CI = Confidence Interval; NS = Not significant.

[a] Statistical analyses done by G type; if more than one rotavirus type was detected from a rotavirus gastroenteritis episode, the episode was counted in each of the detected rotavirus type categories.

[b] Statistically significant versus placebo (P <0.05).

[c] The P genotype was not typeable for one episode.

[d] P[8] genotype was not detected in one episode.

[e] Two cases of G12P[8] were isolated in the second season (one in each group).

15 REFERENCES

1. Murphy TV, Gargiullo PM, Massoudi MS, et al. Intussusception among infants given an oral rotavirus vaccine. *N Engl J Med* 2001;344:564–572.
2. Carlin JB, Macartney KK, Lee KJ, et al. Intussusception Risk and Disease Prevention Associated with Rotavirus Vaccines in Australia's National Immunization Program. *CID* 2013;57(10):1427-1434.
3. Patel MM, López-Collada VR, Bulhões MM, et al. Intussusception Risk and Health Benefits of Rotavirus Vaccination in Mexico and Brazil. *N Engl J Med* 2011;364:2283-2292.
4. Farrington CP, Whitaker HJ, Hocine MN, et al. Case series analysis for censored, perturbed, or curtailed post-event exposures. *Biostatistics* 2009;10(1):3–16.
5. Tate JE, Simonsen L, Viboud C, et al. Trends in intussusception hospitalizations among US infants, 1993–2004: implications for monitoring the safety of the new rotavirus vaccination program. *Pediatrics* 2008;121:e1125-e1132.
6. Centers for Disease Control and Prevention. Prevention of rotavirus gastroenteritis among infants and children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2006;55(No. RR-12):1-13.
7. Parashar UD, Holman RC, Clarke MJ, et al. Hospitalizations associated with rotavirus diarrhea in the United States, 1993 through 1995: surveillance based on the new ICD-9-CM rotavirus-specific diagnostic code. *J Infect Dis* 1998;177:13-17.
8. Ruuska T, Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for severity of diarrheal episodes. *Scand J Infect Dis* 1990;22:259-267.

16 HOW SUPPLIED/STORAGE AND HANDLING

ROTARIX is available in single-dose vials of lyophilized vaccine, accompanied by a prefilled oral applicator of liquid diluent (1 mL) with a plunger stopper, and a transfer adapter for reconstitution.

Supplied as an outer package of 10 doses (NDC 58160-854-52) containing:

NDC 58160-851-01 vial of lyophilized vaccine in package of 10: NDC 58160-851-10

NDC 58160-853-02 oral applicator of diluent (10 applicators)

16.1 Storage before Reconstitution

- Lyophilized vaccine in vials: Store refrigerated at 2° to 8°C (36° to 46°F). **Protect vials from light.**
- Diluent in oral applicators: Store refrigerated at 2° to 8°C (36° to 46°F) or at a controlled room temperature up to 25°C (77°F). **Do not freeze. Discard if the diluent has been frozen.**

16.2 Storage after Reconstitution

ROTARIX should be administered within 24 hours of reconstitution. After reconstitution, store refrigerated at 2° to 8°C (36° to 46°F) or at a controlled room temperature up to 25°C (77°F). Discard the reconstituted vaccine in biological waste container if not used within 24 hours. **Do not freeze. Discard if the reconstituted vaccine has been frozen.**

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information). Patient labeling is provided as a tear-off leaflet at the end of this full prescribing information.

- Parents or guardians should be informed by the healthcare provider of the potential benefits and risks of immunization with ROTARIX, and of the importance of completing the immunization series.
- The healthcare provider should inform the parents or guardians about the potential for adverse reactions that have been temporally associated with administration of ROTARIX or other vaccines containing similar components.
- The parent or guardian should immediately report any signs and/or symptoms of intussusception.
- The parent or guardian should be given the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

ROTARIX and PEDIARIX are registered trademarks of the GSK group of companies.

Manufactured by **GlaxoSmithKline Biologicals**

Rixensart, Belgium, US License 1617

Distributed by **GlaxoSmithKline**

Research Triangle Park, NC 27709

©YEAR the GSK group of companies. All rights reserved.

RTX:XXPI

PATIENT INFORMATION
ROTARIX® (ROW-tah-rix)
Rotavirus Vaccine, Live, Oral

Read this Patient Information carefully before your baby gets ROTARIX and before your baby receives the next dose of ROTARIX. This leaflet is a summary of information about ROTARIX and does not take the place of talking with your baby's doctor.

What is ROTARIX?

ROTARIX is a vaccine that protects your baby from a kind of virus (called a rotavirus) that can cause bad diarrhea and vomiting. Rotavirus can cause diarrhea and vomiting that is so bad that your baby can lose too much body fluid and need to go to the hospital.

Rotavirus vaccine is a liquid that is given to your baby by mouth. It is not a shot.

Who should not take ROTARIX?

Your baby should not get ROTARIX if:

- He or she has had an allergic reaction after getting a dose of ROTARIX.
- He or she is allergic to any of the ingredients of this vaccine. A list of ingredients can be found at the end of this leaflet.
- A doctor has told you that your baby's digestive system has a defect (is not normal).
- He or she has a history of a serious problem called intussusception that happens when a part of the intestine gets blocked or twisted.
- He or she has Severe Combined Immunodeficiency Disease (SCID), a severe problem with his/her immune system.

Tell your doctor if your baby:

- Is allergic to latex.
- Has problems with his/her immune system.
- Has cancer.
- Will be in close contact with someone who has problems with his/her immune system or is getting treated for cancer as the spread of vaccine virus to non-vaccinated contacts could occur. Hand washing is recommended after diaper changes to help prevent the spread of vaccine virus.

If your baby has been having diarrhea and vomiting, your doctor may want to wait before giving your baby a dose of ROTARIX.

What are possible side effects of ROTARIX?

The most common side effects of ROTARIX are:

- Crying
- Fussiness
- Cough
- Runny nose
- Fever
- Loss of appetite
- Vomiting.

Call your doctor right away or go to the emergency department if your baby has any of these problems after getting ROTARIX, even if it has been several weeks since the last vaccine dose because these may be signs of a serious problem called intussusception:

- Bad vomiting
- Bad diarrhea
- Bloody bowel movement
- High fever
- Severe stomach pain (if your baby brings his/her knees to his/her chest while crying or screaming).

Studies showed an increased risk of intussusception after the first and second dose of vaccine, especially in the first 7 days.

Since FDA approval, reports of infants with intussusception have been received by Vaccine Adverse Event Reporting System (VAERS). Intussusception occurred days and sometimes weeks after vaccination. Some infants needed hospitalization, surgery on their intestines, or a special enema to treat this problem. Death due to intussusception has occurred.

Other reported side effects include: Kawasaki disease (a serious condition that can affect the heart; symptoms may include fever, rash, red eyes, red mouth, swollen glands, swollen hands, and feet and, if not treated, death can occur).

Talk to your baby's doctor if your baby has any problems that concern you.

How is ROTARIX given?

ROTARIX is a liquid that is dropped into your baby's mouth and swallowed.

Figure 1. Administration of ROTARIX

Your baby will get the first dose at around 6 weeks old.

The second dose will be at least 4 weeks after the first dose (before 6 months old).

Be sure to plan the time for your baby's second dose with the doctor because it is important that your baby gets both doses of ROTARIX before your baby is 6 months old.

The doctor may decide to give your baby shots at the same time as ROTARIX.

Your baby can be fed normally after getting ROTARIX.

What are the ingredients in ROTARIX?

ROTARIX contains weakened human rotavirus.

ROTARIX also contains dextran, sorbitol, xanthan, and Dulbecco's Modified Eagle Medium (DMEM). The ingredients of DMEM are as follows: sodium chloride, potassium chloride, magnesium sulphate, ferric (III) nitrate, sodium phosphate, sodium pyruvate, D-glucose, concentrated vitamin solution, L-cystine, L-tyrosine, amino acids solution, L-glutamine, calcium chloride, sodium hydrogenocarbonate, and phenol red.

Porcine circovirus type 1 (PCV-1), a virus found in pigs, is present in ROTARIX. PCV-1 is not known to cause disease in humans.

ROTARIX contains no preservatives.

The dropper used to give your baby ROTARIX contains latex.

ROTARIX is a registered trademark of the GSK group of companies.

gsk GlaxoSmithKline

Manufactured by **GlaxoSmithKline Biologicals**

Rixensart, Belgium, US License 1617

Distributed by **GlaxoSmithKline**

Research Triangle Park, NC 27709

©YEAR the GSK group of companies. All rights reserved.

Month YEAR

RTX:XXPIL