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) in infants and children. (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----------

History of uncorrected congenital malformation of the gastrointestinal tract that would predispose the infant to intussusception. (4)

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

- Previous hypersensitivity to any component of ROTARIX including latex rubber (contained in oral applicator). (5.1, 11)
- 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)
- Since ROTARIX is a live virus safety and effectiveness in infants with known primary or secondary immunodeficiencies have not been evaluated. (5.3)

---------- 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: May 2009
RTX:4PI

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 in infants and children *[see Clinical Studies (14.3)]*.

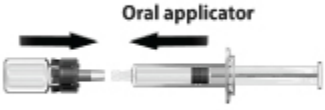
2 DOSAGE AND ADMINISTRATION

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. Inspect vials visually for any cracks prior to administration. If any cracks exist, the vaccine should not be administered.

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

Breast-feeding was permitted in clinical studies. There was no evidence to suggest that breast-feeding 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

History of uncorrected congenital malformation of the gastrointestinal tract (such as Meckel's diverticulum) that would predispose the infant for intussusception.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Review infant immunization history for hypersensitivity and other reactions to any component of ROTARIX, including latex rubber contained in the oral applicator. *[See Description (11).]*

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).]*

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 evaluated.

5.4 Shedding and Transmission

Rotavirus shedding in stool occurs after vaccination with peak excretion occurring around day 7 after dose 1. Live rotavirus shedding was evaluated in two studies among a subset of infants at day 7 after dose 1. In these studies, the estimated percentages of recipients of ROTARIX who shed live rotavirus were 25.6% (95% Confidence Interval [CI]: 10.2, 41.1) and 26.5% (95% CI: 15.5, 37.5), respectively. Transmission of virus was not evaluated. There is a possibility that the live vaccine virus can be transmitted to non-vaccinated contacts. The potential for transmission of vaccine virus following vaccination should be weighed against the possibility of acquiring and transmitting natural rotavirus.

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 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).]*

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 to 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*	52	52	42	42
Cough/runny nose†	28	30	31	33
Fever‡	25	33	28	34
Loss of appetite§	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.
* Defined as crying more than usual.
† 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.
‡ Defined as temperature ≥100.4°F (≥38.0°C) rectally or ≥99.5°F (≥37.5°C) orally.
§ 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% 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 of diagnosis after any dose	6	7
Relative Risk (95% CI)	0.85 (0.30, 2.42)	
Within 100 days of dose 1*	9	16
Relative Risk (95% CI)	0.56 (0.25, 1.24)	

CI = Confidence Interval.

* 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: two 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 following adverse events have been reported since market introduction of ROTARIX outside the U.S. 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.

Blood and Lymphatic System Disorders: Idiopathic thrombocytopenic purpura.

Gastrointestinal Disorders: Hematochezia, intussusception.

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 Combined], 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. 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 contains no preservatives.

The tip cap and the rubber plunger of the oral applicator contain dry natural latex rubber. The vial stopper and transfer adapter are latex-free.

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.[2] Among children up to 3 years of age, approximately 16% of cases before 6 months of age result in hospitalization.[3]

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 two 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.

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. Breast-feeding 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.[4]

The primary efficacy endpoint was prevention of any grade of severity 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*		Total Vaccinated Cohort†	
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‡	5	60	5	64
Efficacy estimate against RV GE				
Any severity	87.1%§		87.3%§	
(95% CI)	(79.6, 92.1)		(80.3, 92.0)	
Severe‡	95.8%§		96.0%§	
(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%§		100%§	
(95% CI)	(81.8, 100)		(81.7, 100)	

RV GE = rotavirus gastroenteritis; CI = Confidence Interval.

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

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

‡ Severe gastroenteritis defined as ≥11 on the Vesikari scale.

§ Statistically significant vs. 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 the age of 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*		**Total Vaccinated Cohort†**	
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 (95% CI)	84.7%‡ (71.7, 92.4)		81.1%‡ (68.5, 89.3)	
Cases of hospitalization due to RV GE	9	59	14	72
Efficacy in reducing hospitalizations due to RV GE (95% CI)	85.0%‡ (69.6, 93.5)		80.8%‡ (65.7, 90.0)	

RV GE = rotavirus gastroenteritis; CI = Confidence Interval.

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

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

‡ Statistically significant vs. 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[*]	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%[†] (87.9, 98.8)	18	89[‡,§]	89.8%[†] (82.9, 94.2)
G2P[4]	3	4[‡]	NS	14	17[‡]	58.3%[†] (10.1, 81.0)
G3P[8]	1	5	89.9%[†] (9.5, 99.8)	3	10	84.8%[†] (41.0, 97.3)
G4P[8]	3	13	88.3%[†] (57.5, 97.9)	6	18	83.1%[†] (55.6, 94.5)
G9P[8]	13	27	75.6%[†] (51.1, 88.5)	38	71[§]	72.9%[†] (59.3, 82.2)
Combined non-G1 (G2, G3, G4, G9, G12) types[‖]	20	49	79.3%[†] (64.6, 88.4)	62	116	72.9%[†] (62.9, 80.5)
SEVERE						
G1P[8]	2	28	96.4%[†] (85.7, 99.6)	4	57	96.4%[†] (90.4, 99.1)
G2P[4]	1	2[‡]	NS	2	7[‡]	85.5%[†] (24.0, 98.5)
G3P[8]	0	5	100%[†] (44.8, 100)	1	8	93.7%[†] (52.8, 99.9)
G4P[8]	0	7	100%[†] (64.9, 100)	1	11	95.4%[†] (68.3, 99.9)
G9P[8]	2	19	94.7%[†] (77.9, 99.4)	13	44[§]	85.0%[†] (71.7, 92.6)
Combined non-G1 (G2, G3, G4, G9, G12) types[‖]	3	33	95.4%[†] (85.3, 99.1)	17	70	87.7%[†] (78.9, 93.2)

CI = Confidence Interval; NS = Not significant.

[*] 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.

[†] Statistically significant vs. placebo ($p<0.05$).

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

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

[‖] 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. 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.
3. 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.
4. 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 as a vial of lyophilized vaccine, a prefilled oral applicator of liquid diluent (1 mL) with a plunger stopper, and a transfer adapter for reconstitution.

Supplied as:

NDC 58160-805-11 (package of 10)

16.1 Storage Before Reconstitution

- Vials: Store the vials of lyophilized ROTARIX refrigerated at 2° to 8°C (36° to 46°F). **Protect vials from light.**
- Diluent: The diluent may be stored at a controlled room temperature 20° to 25°C (68° to 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. It may be stored refrigerated at 2° to 8°C (36° to 46°F) or at room temperature up to 25°C (77°F), after reconstitution. Discard the reconstituted vaccine if not used within 24 hours in biological waste container. **Do not freeze. Discard if the vaccine has been frozen.**

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (17.2).

17.1 Patient Advice

- 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 accompanying the recipient should be instructed to report any adverse events to their healthcare provider.
- 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).

17.2 FDA-Approved Patient Labeling

Patient labeling is provided as a tear-off leaflet at the end of this full prescribing information.

ROTARIX and PEDIARIX are registered trademarks of GlaxoSmithKline.

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Research Triangle Park, NC 27709

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 a doctor has told you that your baby's digestive system has a defect (is not normal).

Tell your doctor if your baby:

- Has had an allergic reaction to the last dose of ROTARIX.
- Is allergic to any ingredient of ROTARIX or 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.

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

Call your child's doctor right away if your child has vomiting, diarrhea, severe stomach pain, severe crying, blood in their stool or change in his/her bowel movements as these may be signs of a serious problem called intussusception. It is important to contact your doctor if you have questions or if your child has any of these symptoms, even if it has been several weeks since the last vaccine dose.

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 possible side effects of ROTARIX?

The most common side effects of ROTARIX are:

- Crying
- Fussy
- 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 because these may be signs of a serious problem:

- 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).

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

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. ROTARIX contains no preservatives.

The dropper used to give your baby ROTARIX contains latex.

ROTARIX is a registered trademark of GlaxoSmithKline.

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October 2008
RTX:2PIL