

## 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<sub>50</sub>) 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 ( $\geq 5\%$ ) 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](http://www.vaers.hhs.gov).

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

Revised: xx/xxxx

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

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1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

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

6 **2 DOSAGE AND ADMINISTRATION**

7 **2.1 Reconstitution Instructions for Oral Administration**

8 **For oral use only.** Not for injection.

9 Reconstitute only with accompanying diluent. Do not mix ROTARIX with other vaccines or  
10 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.

## 11 **2.2 Recommended Dose and Schedule**

12 The vaccination series consists of two 1-mL doses administered **orally**. The first dose should be  
13 administered to infants beginning at 6 weeks of age. There should be an interval of at least  
14 4 weeks between the first and second dose. The 2-dose series should be completed by 24 weeks  
15 of age.

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

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

## 20 **2.3 Infant Feeding**

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

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

### 25 **3 DOSAGE FORMS AND STRENGTHS**

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

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

### 30 **4 CONTRAINDICATIONS**

#### 31 **4.1 Hypersensitivity**

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

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

#### 35 **4.2 Gastrointestinal Tract Congenital Malformation**

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

#### 39 **4.3 History of Intussusception**

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

#### 44 **4.4 Severe Combined Immunodeficiency Disease**

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

### 49 **5 WARNINGS AND PRECAUTIONS**

#### 50 **5.1 Latex**

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

53 **5.2 Gastrointestinal Disorders**

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

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

58 **5.3 Altered Immunocompetence**

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

63 **5.4 Shedding and Transmission**

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

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

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

73 **5.5 Intussusception**

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

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

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

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

88 **5.6 Post-exposure Prophylaxis**

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

91 **6 ADVERSE REACTIONS**

92 **6.1 Clinical Trials Experience**

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

98 Solicited and unsolicited adverse events, serious adverse events and cases of intussusception  
99 were collected in 7 clinical studies. Cases of intussusception and serious adverse events were  
100 collected in an additional large safety study. These 8 clinical studies evaluated a total of 71,209  
101 infants who received ROTARIX (N = 36,755) or placebo (N = 34,454). The racial distribution  
102 for these studies was as follows: Hispanic 73.4%, white 16.2%, black 1.0%, and other 9.4%;  
103 51% were male.

104 Solicited Adverse Events

105 In 7 clinical studies, detailed safety information was collected by parents/guardians for 8  
106 consecutive days following vaccination with ROTARIX (i.e., day of vaccination and the next  
107 7 days). A diary card was completed to record fussiness/irritability, cough/runny nose, the  
108 infant's temperature, loss of appetite, vomiting, or diarrhea on a daily basis during the first week  
109 following each dose of ROTARIX or placebo. Adverse events among recipients of ROTARIX  
110 and placebo occurred at similar rates (Table 1).

111 **Table 1. Solicited Adverse Events within 8 Days Following Doses 1 and 2 of ROTARIX or**  
 112 **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 <sup>a</sup>	52	52	42	42
Cough/runny nose <sup>b</sup>	28	30	31	33
Fever <sup>c</sup>	25	33	28	34
Loss of appetite <sup>d</sup>	25	25	21	21
Vomiting	13	11	8	8
Diarrhea	4	3	3	3

113 Total vaccinated cohort = All vaccinated infants for whom safety data were available.

114 N = Number of infants for whom at least one symptom sheet was completed.

115 <sup>a</sup> Defined as crying more than usual.

116 <sup>b</sup> Data not collected in 1 of 7 studies; Dose 1: ROTARIX N = 2,583; placebo N = 1,897;  
 117 Dose 2: ROTARIX N = 2,522; placebo N = 1,863.

118 <sup>c</sup> Defined as temperature  $\geq 100.4^{\circ}\text{F}$  ( $\geq 38.0^{\circ}\text{C}$ ) rectally or  $\geq 99.5^{\circ}\text{F}$  ( $\geq 37.5^{\circ}\text{C}$ ) orally.

119 <sup>d</sup> Defined as eating less than usual.

## 120 Unsolicited Adverse Events

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

## 127 Serious Adverse Events (SAEs)

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

## 135 Deaths

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

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

141 **Intussusception**

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

149 No increased risk of intussusception following administration of ROTARIX was observed within  
 150 a 31-day period following any dose, and rates were comparable to the placebo group after a  
 151 median of 100 days (Table 2). In a subset of 20,169 infants (10,159 received ROTARIX and  
 152 10,010 received placebo) followed up to one year after Dose 1, there were 4 cases of  
 153 intussusception with ROTARIX compared with 14 cases of intussusception with placebo  
 154 (Relative Risk: 0.28 [95% CI: 0.10, 0.81]). All of the infants who developed intussusception  
 155 recovered without sequelae.

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

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

157 CI = Confidence Interval.

158 <sup>a</sup> Median duration after Dose 1 (follow-up visit at 30 to 90 days after Dose 2).

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



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

Day Range	Dose 1		Dose 2		Any Dose	
	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
<b>Total (0-30)</b>	1	2	5	5	6	7

163 **Kawasaki Disease**

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

173 **6.2 Postmarketing Experience**

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

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

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

191 Mexico study does exist in US infants, it is estimated that approximately 1 to 3 additional cases  
192 of intussusception hospitalizations would occur per 100,000 vaccinated infants in the US within  
193 7 days following the first dose of ROTARIX. In the first year of life, the background rate of  
194 intussusception hospitalizations in the US has been estimated to be approximately 34 per  
195 100,000 infants.<sup>5</sup>

196 Other postmarketing observational studies conducted in Brazil and Australia also suggest an  
197 increased risk of intussusception within the first 7 days following the second dose of  
198 ROTARIX.<sup>2,3</sup>

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

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

#### 205 Gastrointestinal Disorders

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

#### 208 Blood and Lymphatic System Disorders

209 Idiopathic thrombocytopenic purpura.

#### 210 Vascular Disorders

211 Kawasaki disease.

#### 212 General Disorders and Administration Site Conditions

213 Maladministration.

## 214 **7 DRUG INTERACTIONS**

### 215 **7.1 Concomitant Vaccine Administration**

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

223 **7.2 Immunosuppressive Therapies**

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

227 **8 USE IN SPECIFIC POPULATIONS**

228 **8.1 Pregnancy**

229 Pregnancy Category C

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

233 **8.4 Pediatric Use**

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

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

242 **11 DESCRIPTION**

243 ROTARIX (Rotavirus Vaccine, Live, Oral), for oral administration, is a live, attenuated rotavirus  
244 vaccine derived from the human 89-12 strain which belongs to G1P[8] type. The rotavirus strain  
245 is propagated on Vero cells. After reconstitution, the final formulation (1 mL) contains at least  
246  $10^{6.0}$  median Cell Culture Infective Dose (CCID<sub>50</sub>) of live, attenuated rotavirus.

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

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

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

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

261 ROTARIX contains no preservatives.

## 262 **12 CLINICAL PHARMACOLOGY**

### 263 **12.1 Mechanism of Action**

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

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

### 271 **12.2 Pharmacodynamics**

#### 272 Immunogenicity

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

#### 280 Shedding and Transmission

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

290 Transmitted vaccine virus was identified in 15 of 80 twins receiving placebo (18.8% [95% CI:  
291 10.9, 29.0]). Median duration of the rotavirus shedding was 10 days in twins who received  
292 ROTARIX as compared with 4 days in twins who received placebo in whom the vaccine virus

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

## 295 **13 NONCLINICAL TOXICOLOGY**

### 296 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

## 299 **14 CLINICAL STUDIES**

### 300 **14.1 Efficacy Studies**

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

306 A randomized, double-blind, placebo-controlled study was conducted in 6 European countries. A  
307 total of 3,994 infants were enrolled to receive ROTARIX (n = 2,646) or placebo (n = 1,348).

308 Vaccine or placebo was given to healthy infants as a 2-dose series with the first dose  
309 administered orally from 6 through 14 weeks of age followed by one additional dose  
310 administered at least 4 weeks after the first dose. The 2-dose series was completed by 24 weeks  
311 of age. For both vaccination groups, 98.3% of infants were white and 53% were male.

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

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

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

329 92.0). Efficacy against severe rotavirus gastroenteritis through one rotavirus season was 95.8%  
 330 (95% CI: 89.6, 98.7); TVC efficacy was 96.0% (95% CI: 90.2, 98.8) (Table 4). The protective  
 331 effect of ROTARIX against any grade of severity of rotavirus gastroenteritis observed  
 332 immediately following Dose 1 administration and prior to Dose 2 was 89.8% (95% CI: 8.9,  
 333 99.8).

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

338 **Table 4. Efficacy Evaluation of ROTARIX through One Rotavirus Season**

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

339 RV GE = Rotavirus gastroenteritis; CI = Confidence Interval.

340 <sup>a</sup> ATP analysis includes all infants in the efficacy cohort who received two doses of vaccine  
 341 according to randomization.

342 <sup>b</sup> TVC analysis includes all infants in the efficacy cohort who received at least one dose of  
 343 vaccine or placebo.

344 <sup>c</sup> Severe gastroenteritis defined as  $\geq 11$  on the Vesikari scale.

345 <sup>d</sup> Statistically significant versus placebo ( $P < 0.001$ ).

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

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

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

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

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

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

369 **Table 5. Efficacy Evaluation of ROTARIX through One Year**

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

370 RV GE = Rotavirus gastroenteritis; CI = Confidence Interval.

371 <sup>a</sup> ATP analysis includes all infants in the efficacy cohort who received two doses of vaccine  
 372 according to randomization.

373 <sup>b</sup> TVC analysis includes all infants in the efficacy cohort who received at least one dose of  
 374 vaccine or placebo.

375 <sup>c</sup> Statistically significant versus placebo ( $P < 0.001$ ).

376 **14.2 Efficacy through Two Rotavirus Seasons**

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

379 In the European study, the efficacy of ROTARIX against any grade of severity of rotavirus  
380 gastroenteritis through two rotavirus seasons was 78.9% (95% CI: 72.7, 83.8). Efficacy in  
381 preventing any grade of severity of rotavirus gastroenteritis cases occurring only during the  
382 second season post-vaccination was 71.9% (95% CI: 61.2, 79.8). The efficacy of ROTARIX  
383 against severe rotavirus gastroenteritis through two rotavirus seasons was 90.4% (95% CI: 85.1,  
384 94.1). Efficacy in preventing severe rotavirus gastroenteritis cases occurring only during the  
385 second season post-vaccination was 85.6% (95% CI: 75.8, 91.9).

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

388 In the Latin American study, the efficacy of ROTARIX against severe rotavirus gastroenteritis  
389 through two years was 80.5% (95% CI: 71.3, 87.1). Efficacy in preventing severe rotavirus  
390 gastroenteritis cases occurring only during the second year post-vaccination was 79.0% (95% CI:  
391 66.4, 87.4). The efficacy of ROTARIX in reducing hospitalizations for rotavirus gastroenteritis  
392 through two years was 83.0% (95% CI: 73.1, 89.7).

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

394 **14.3 Efficacy against Specific Rotavirus Types**

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



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

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

403 CI = Confidence Interval; NS = Not significant.

404 <sup>a</sup> Statistical analyses done by G type; if more than one rotavirus type was detected from a rotavirus gastroenteritis  
 405 episode, the episode was counted in each of the detected rotavirus type categories.

406 <sup>b</sup> Statistically significant versus placebo ( $P < 0.05$ ).

407 <sup>c</sup> The P genotype was not typeable for one episode.

408 <sup>d</sup> P[8] genotype was not detected in one episode.

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

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430 severity of diarrheal episodes. *Scand J Infect Dis* 1990;22:259-267.

431 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

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

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

438 **16.1 Storage before Reconstitution**

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

443 **16.2 Storage after Reconstitution**

444 ROTARIX should be administered within 24 hours of reconstitution. After reconstitution, store  
445 refrigerated at 2° to 8°C (36° to 46°F) or at a controlled room temperature up to 25°C (77°F).

446 Discard the reconstituted vaccine in biological waste container if not used within 24 hours. **Do**  
447 **not freeze. Discard if the reconstituted vaccine has been frozen.**

448 **17 PATIENT COUNSELING INFORMATION**

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

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

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



464

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**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.

506 **What are possible side effects of ROTARIX?**

507 The most common side effects of ROTARIX are:

- 508 • Crying
- 509 • Fussiness
- 510 • Cough
- 511 • Runny nose
- 512 • Fever
- 513 • Loss of appetite
- 514 • Vomiting.

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

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

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

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

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

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

536 **How is ROTARIX given?**

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

538 **Figure 1. Administration of ROTARIX**



539

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

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

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

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

546 Your baby can be fed normally after getting ROTARIX.

547 **What are the ingredients in ROTARIX?**

548 ROTARIX contains weakened human rotavirus.

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

555 Porcine circovirus type 1 (PCV-1), a virus found in pigs, is present in ROTARIX.

556 PCV-1 is not known to cause disease in humans.

557 ROTARIX contains no preservatives.

558 The dropper used to give your baby ROTARIX contains latex.

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



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