

## PRODUCT MONOGRAPH

### **ROTARIX™**

Human rotavirus, live, attenuated, oral vaccine

Oral suspension

Active immunizing agent

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## ROTARIX™

Human rotavirus, live, attenuated, oral vaccine

### PART I: HEALTH PROFESSIONAL INFORMATION

#### SUMMARY PRODUCT INFORMATION

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
Oral	Suspension/not less than $10^{6.0}$ CCID <sub>50</sub> of human rotavirus RIX4414 strain, per 1.5 mL dose.	Dulbecco's Modified Eagle Medium (DMEM), sucrose, di-sodium adipate, sterile water.  <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

#### DESCRIPTION

ROTARIX™ (human rotavirus, live, attenuated, oral vaccine) is a suspension presented in monodose oral applicators for oral administration. The vaccine includes an antacid component to protect the vaccine during passage through the stomach and prevent its inactivation due to acidic environment.

#### INDICATIONS AND CLINICAL USE

ROTARIX™ is indicated for active immunization of infants from the age of 6 weeks for the prevention of gastroenteritis caused by rotavirus types G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8].

The results from the clinical trials suggest that the vaccine's efficacy may vary with the type of rotavirus causing the infection (see Part II CLINICAL TRIALS section).

## CONTRAINDICATIONS

ROTARIX™ should not be administered in:

- Infants who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- Infants who experienced hypersensitivity after previous administration of rotavirus vaccines.
- Infants with uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for intussusception.

## WARNINGS AND PRECAUTIONS

### General

It is good clinical practice that vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

As with other vaccines, administration of ROTARIX™ should be postponed in infants suffering from acute severe febrile illness. However, the presence of a minor infection such as a cold should not result in the deferral of vaccination.

No safety or efficacy data are available for the administration of ROTARIX™ to:

- Individuals who have received a blood transfusion or blood products, including immunoglobulins, within 42 days.

No efficacy data are available for the administration of ROTARIX™ to:

- Immunocompromised patients such as individuals with malignancies receiving immunosuppressive therapy or who are otherwise immunocompromised.

The administration of ROTARIX™ should be postponed in infants suffering from diarrhea or vomiting.

Excretion of the vaccine virus in the stools is known to occur after vaccination with peak excretion around the 7th day. Viral antigen particles detected by ELISA were found in 50% (at day 7) of stools after the first dose and 17.4% (at day 3) and 4% (at day 7) of stools after the second dose. When these stools were tested for the presence of live vaccine strain, only 17% were positive.

Contacts of recent vaccinees should be advised to observe personal hygiene (e.g. wash their hands after changing child's diapers).

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

ROTARIX™ does not protect against gastroenteritis due to other pathogens than rotavirus.

No data are available on the use of ROTARIX™ for post-exposure prophylaxis.

**UNDER NO CIRCUMSTANCES SHOULD ROTARIX™ BE INJECTED.**

### **Gastrointestinal**

There are no data on the safety and efficacy of ROTARIX™ in infants with gastrointestinal illnesses. Administration of ROTARIX™ may be considered with caution in such infants when, in the opinion of the physician, withholding the vaccine entails a greater risk.

### **Immune**

In some clinical trials, ROTARIX™ was not administered to infants known to have immunodeficient household members. There is a theoretical risk that the live virus vaccine can be transmitted to non-vaccinate contacts. Therefore, ROTARIX™ should be administered with caution to individuals known to have immunodeficient close contacts such as:

- Individuals with malignancies or who are otherwise immunocompromised; or
- Individuals receiving immunosuppressive therapy.

However, because nearly all children are infected with naturally occurring rotavirus by the age of 5 years, vaccination of infants may decrease the risk of exposure of immunodeficient household contacts to naturally occurring rotavirus. The health care provider should assess the potential risks and benefits of administering ROTARIX™ to infants known to have immunodeficient close contacts.

Asymptomatic and mildly symptomatic HIV infections are not expected to affect the safety or efficacy of ROTARIX™. A clinical study in a limited number of asymptomatic or mildly symptomatic HIV positive infants showed no apparent safety problems (see ADVERSE REACTIONS, Safety in Infants with Human Immunodeficiency [HIV] Infection). Administration of ROTARIX™ in immunosuppressed infants, including infants on immunosuppressive therapy, should be based on careful consideration of potential benefits and risks.

### **Sensitivity/Resistance**

The vaccine contains 1073 mg of sucrose as an excipient. This amount is too low to cause adverse events in patients with rare hereditary problems such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency.

## **Special Populations**

**Breastfeeding Infants:** Evidence from some clinical trials with ROTARIX™ suggest breastfeeding does not reduce the protection against rotavirus gastroenteritis afforded by ROTARIX™. Therefore breastfeeding may be continued during the vaccination schedule.

**Pregnant Women:** ROTARIX™ is not intended for use in adults. Thus, human data on use during pregnancy are not available and animal reproduction studies have not been performed.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

- **Clinical trials for the lyophilized formulation**

In a total of eleven placebo controlled clinical trials, approximately 80,000 doses of ROTARIX™ were administered to approximately 40,200 infants.

In two clinical trials (Finland), ROTARIX™ lyophilized formulation was administered alone (administration of routine pediatric vaccines was staggered). The incidence and severity of diarrhea, vomiting, loss of appetite, fever and irritability was not different in the group receiving ROTARIX™ when compared to the group receiving placebo. No increase in the incidence or severity of these reactions was seen with the second dose.

In the remaining nine trials (Europe, Canada, USA, Latin America, Singapore, South Africa), ROTARIX™ lyophilized formulation was coadministered with routine paediatric vaccines (see DRUG INTERACTIONS). The adverse reaction profile observed in these subjects was similar to the adverse reaction profile observed in subjects receiving the same pediatric vaccines and placebo.

### **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

### **Intussusception**

The risk of intussusception has been evaluated in a large safety trial conducted in Latin America and Finland where 63,225 subjects were enrolled. No increased risk of

intussusception in the ROTARIX™ group was observed and observed rates were comparable to the placebo group. Data are shown below in Tables 1 and 2.

**Table 1 Rate of intussusception within 31 days after administration**

Intussusception	ROTARIX™	Placebo	Relative risk (95% CI)
	N=31,673	N=31,552	
First dose	1	2	0.50 (0.07;3.80)
Second dose	5	5	0.99 (0.31;3.21)

CI: Confidence Interval

**Table 2 Rate of intussusception up to one year of age**

Intussusception	ROTARIX™	Placebo	Relative Risk (95% CI)
	N=10,159	N=10,010	
First dose up to one year	4	14	0.28 (0.10;0.81)

CI: Confidence Interval

In 11 other clinical studies (N =12,220) there were 7 cases of intussusception reported, 5 IS cases in HRV vaccinees and 2 cases in placebo recipient. It is to be highlighted that none of these studies were powered to compare the incidence of intussusception in the ROTARIX™ and placebo groups.

### **Solicited adverse reactions**

In study Rota-036, 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 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 reactions among recipients of ROTARIX™ and placebo occurred at similar rates. See Table 3 below.

**Table 3 Percentage of subjects with each solicited general symptom assessed as causally related to vaccination, reported from Day 0 to Day 7 after each HRV vaccine/placebo dose – Rota-036 Pooled countries (Czech Republic, Finland, France, Germany, Italy and Spain)**

Symptom	ROTARIX™					Placebo				
	N	n	%	95 % CI		N	n	%	95 % CI	
				LL	UL				LL	UL
<b>Dose 1</b>										
Cough/Runny nose	914	58	6.3	4.9	8.1	490	29	5.9	4.0	8.4
Diarrhea	914	18	2.0	1.2	3.1	490	7	1.4	0.6	2.9
Fever	914	133	14.6	12.3	17.0	490	67	13.7	10.8	17.0
Irritability/Fussiness	914	299	32.7	29.7	35.9	490	171	34.9	30.7	39.3
Loss of appetite	914	126	13.8	11.6	16.2	490	71	14.5	11.5	17.9
Vomiting	914	44	4.8	3.5	6.4	490	24	4.9	3.2	7.2
<b>Dose 2</b>										
Cough/Runny nose	905	53	5.9	4.4	7.6	486	34	7.0	4.9	9.6
Diarrhea	905	6	0.7	0.2	1.4	486	8	1.6	0.7	3.2
Fever	905	164	18.1	15.7	20.8	486	95	19.5	16.1	23.4
Irritability/Fussiness	905	238	26.3	23.5	29.3	486	123	25.3	21.5	29.4
Loss of appetite	905	118	13.0	10.9	15.4	486	57	11.7	9.0	14.9
Vomiting	905	18	2.0	1.2	3.1	486	23	4.7	3.0	7.0

N = number of subjects having received the considered dose of HRV vaccine/placebo

n/% = number/percentage of subjects with the specified symptom reported for the considered dose

95% CI: exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Statistically significant differences were not detected between groups for the comparison between ROTARIX™ and Placebo groups for the percentage of subjects with each specified solicited symptom (any, grade 3 and related) reported from Day 0 to Day 7 after any ROTARIX™/placebo doses (P-value > 0.05 for each comparison).

### **Unsolicited Adverse Events (pooled analysis)**

Infants were monitored for unsolicited adverse reactions that occurred in the 31 day period following vaccination in 8 clinical studies. The following adverse reactions occurred at a statistically higher incidence (P-value < 0.05) among recipients of ROTARIX™ (N = 5,543) as compared with placebo recipients (N = 1,852): Rhinorrhea (ROTARIX™ 1.55%, placebo 3.02%), Pharyngitis (ROTARIX™ 1.86%, placebo 2.00%) and Bronchitis (ROTARIX™ 1.95%, placebo 1.03%). In another study (Rota-036: ROTARIX™ N = 2,646, placebo N = 1,348) the incidence of rhinorrhea, pharyngitis and bronchitis was similar between the ROTARIX™ and placebo groups.

## **Serious Adverse Events (SAEs):**

### *Study Rota-023*

Among the total vaccinated cohort of 63,225 infants in study Rota-023 (31,673 in the HRV group and 31,552 in the placebo group), a total of 1,975 subjects (948 infants in the HRV vaccine group and 1,047 infants in the placebo group) reported at least one SAE (up to 30-90 days post Dose 2). No imbalance was observed between treatment groups for SAEs assessed as related to vaccination by the investigators. The overall SAE profile was in favour of the HRV vaccine with significantly fewer SAEs/hospitalizations reported in the HRV vaccine group compared to the placebo group, especially with respect to preventing GE related SAEs.

In study Rota-023, a potential imbalance between groups was noted for Convulsions reported cases: 16 subjects in ROTARIX™ group (5.1/10,000) versus 6 subjects in the placebo group (1.9/10,000). However, no potential imbalance was noted between groups when SAEs related to "Convulsive disorders" were pooled ('Convulsions', 'Epilepsy', 'Grand mal convulsion', 'Status epilepticus' and 'Tonic convulsion'): 20 subjects in the ROTARIX™ group versus 12 in the placebo group.

### *Other clinical trials*

Infants were monitored for serious adverse events that occurred in the 31 day period following vaccination in 8 clinical studies. In these eight trials, 608 subjects reported at least one SAE (450 in vaccinees and 158 in placebo recipients). The incidence of subjects reporting at least one SAE in the group receiving ROTARIX™ (8.12%, 95% CI: 7.41%; 8.87%) was similar to the incidence in the placebo group (8.53%, 95% CI: 7.30%; 9.90%).

## **Deaths:**

In 8,262 infants enrolled and vaccinated in 10 completed trials, a total of 18 deaths were reported: 12 deaths in ROTARIX™ (0.19%, N=6,290) and 6 in placebo (0.30%, N=1,972). In the large safety study (Rota-023), 99 deaths occurred during the study<sup>a</sup>: 56 in ROTARIX™ group (N=31,673) and 43 in the placebo group (N=31,552). None of the cases were assessed as related to vaccination and no potential imbalance was detected for the 99 fatal cases in terms of overall mortality (P-value = 0.198).

## **Safety in Preterm Infants:**

In a clinical study, 1009 preterm infants were administered ROTARIX™ or placebo (198 were 27-30 weeks gestational age and 801 were 31-36 weeks gestational age). The first dose was administered from 6 weeks after birth. SAEs were observed in 5.1% of recipients of ROTARIX™ as compared to 6.8% of placebo recipients. Similar rates of solicited and unsolicited symptoms were observed in ROTARIX™ and placebo recipients. No cases of intussusception were reported. For premature infants born less than 36 weeks of gestation, and who remain hospitalized at the time of recommended

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<sup>a</sup> up to the data lock point.

administration, close monitoring for at least 48 hours after vaccination could be considered.

**Safety in Infants with Human Immunodeficiency (HIV) Infection**

In a clinical study, 100 infants with HIV infection were administered three doses of ROTARIX™ or placebo. The safety profile was similar between ROTARIX™ and placebo recipients.

**Table 4 Adverse reactions considered by the investigator as being at least possibly related to ROTARIX™ vaccination**

Frequency	Adverse Event	System/Organ Class
Very Common: ≥ 10%	irritability	Psychiatric Disorders
	loss of appetite	Gastrointestinal disorders
Common: ≥ 1% and < 10%	diarrhea, vomiting, flatulence, abdominal pain, regurgitation of food	Gastrointestinal disorders
	fever, fatigue	General disorders and administration site conditions
Uncommon: ≥ 0.1% and < 1%	crying, sleep disorder	Psychiatric Disorders
	somnolence	Nervous system disorders
	constipation	Gastrointestinal disorders
Rare: ≥ 0.01% and < 0.1%	upper respiratory tract infection	Infections and infestations
	hoarseness, rhinorrhea	Respiratory, thoracic and mediastinal disorders
	dermatitis, rash	Skin and subcutaneous tissue disorders
	muscle cramp	Musculoskeletal and connective tissue disorders

- **Clinical trials for the liquid formulation**

In a total of 4 clinical trials, approximately 3800 doses of ROTARIX™ liquid formulation were administered to approximately 1930 infants. Those trials have shown that the safety and reactogenicity profile of the liquid formulation is comparable to the lyophilized formulation.

**Post-Marketing Adverse Drug Reactions**

The following events have been spontaneously reported during post-approval use of ROTARIX™. Because these events were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish a causal relationship to vaccine exposure.

**Gastrointestinal disorders:** Hematochezia, Intussusception.

**Infections and Infestations:** Kawasaki disease

## DRUG INTERACTIONS

### Overview

Immunosuppressive therapies may reduce the immune response to vaccines. The potential interaction of these therapies with ROTARIX™ is not known.

### Use With Other Vaccines

ROTARIX™ can be given concomitantly with any of the following monovalent or combination vaccines [including hexavalent vaccines (DTPa-HBV-IPV/Hib)]: diphtheria-tetanus-whole cell pertussis vaccine (DTPw), diphtheria-tetanus-acellular pertussis vaccine (DTPa), *Haemophilus influenzae* type b vaccine (Hib), inactivated polio vaccine (IPV), hepatitis B vaccine (HBV), pneumococcal conjugate vaccine and meningococcal serogroup C conjugate vaccine. Clinical studies demonstrated that the immune responses to and the safety profiles of the administered vaccines were unaffected.

Concomitant administration of ROTARIX™ and oral polio vaccine (OPV) does not affect the immune response to the polio antigens but may reduce that to ROTARIX™ vaccine. The immune response to ROTARIX™ is unaffected when OPV is administered two weeks apart from ROTARIX™.

## DOSAGE AND ADMINISTRATION

### Dosing Considerations

- ROTARIX™ is for **oral** use only.
- UNDER NO CIRCUMSTANCES SHOULD ROTARIX™ BE INJECTED.

### Recommended Dose and Dosage Adjustment

The vaccination course consists of two doses. The first dose can be administered from the age of 6 weeks. There should be an interval of at least 4 weeks between doses. ROTARIX™ may be given to preterm infants following the same vaccination course. This could be incorporated into the Canadian Immunization Schedule (2 and 4 months). Other immunization schedules have also been evaluated (see CLINICAL TRIALS). The administration of the 2 doses should be completed by the age of 24 weeks.

In particular circumstances, if the vaccine is given at an earlier age, and that the second dose is given within the shortest interval of 4 weeks, a lower immune response might be induced (see CLINICAL TRIALS, Protective efficacy of ROTARIX™ liquid formulation).

It is strongly recommended that infants who receive a first dose of ROTARIX™ complete the 2 dose regimen with ROTARIX™. There are no data on safety, immunogenicity or efficacy when ROTARIX™ is administered for the first dose and another rotavirus vaccine is administered for the second dose or vice versa.

In clinical trials, spitting or regurgitation of the vaccine has rarely been observed and, under such circumstances, a replacement dose was not given. However, in the unlikely event that an infant spits out or regurgitates most of the vaccine dose, a single replacement dose may be given at the same vaccination visit.

There are no restrictions on the infant's consumption of food or liquid, including breastmilk, either before or after vaccination.

There is no evidence available to suggest that breastfeeding would reduce the protection against rotavirus gastroenteritis afforded by ROTARIX™. Therefore, breastfeeding may be continued during the vaccination schedule.

The number of doses that would provide sufficient protection in immune compromised subjects has not been determined.

### **Administration**

See SPECIAL HANDLING INSTRUCTIONS.

### **OVERDOSAGE**

No case of overdose has been reported.

### **ACTION AND CLINICAL PHARMACOLOGY**

Rotavirus infection is the leading cause of severe acute gastroenteritis in infants and young children throughout the world. Rotavirus is transmitted mainly by the fecal-oral route, through close person-to-person contact, and through fomites. Ingested virus particles infect the cells in the villi of the small intestine, typically leading to villous atrophy. Characteristic clinical features include diarrhea, vomiting, fever and abdominal discomfort, occasionally leading to fatal dehydrating illness. Improvements or increased efforts in hygiene and sanitation are known to be of limited efficacy.

Rotavirus infection affects 95% of children by the age of 3 to 5 years worldwide. The incidence of rotavirus infections is highest in children between 6 and 24 months of age. Primary infection after 3 months of age usually causes the most severe disease. Subsequent infections are possible but typically cause much milder symptoms.

The mortality rate associated with rotavirus is estimated to be 611,000 (range 454,000-705,000) annual deaths worldwide. Although the number of deaths due to rotavirus may be underestimated because testing for rotavirus is not routine, the mortality for Canada is proportionally compatible with estimated numbers from the US of 20 to 102 deaths per year. Rotavirus is estimated to cause 39% (range 29% to 45%) of childhood diarrhea hospitalizations.

Morbidity due to hospitalizations for diarrhea caused by rotavirus is high in industrialized countries. Nearly every child in the US is infected with rotavirus by the age of 5 years and the majority will have gastroenteritis, resulting in approximately 410,000 physician visits, 205,000-272,000 emergency department visits and 55,000-70,000 hospitalizations each year.

In Canada, rotavirus gastroenteritis during the winter and spring seasons have been estimated as representing between 37% (Greater Toronto) to 71% (Quebec) of community acquired gastroenteritis cases resulting in hospitalization, in children aged less than 5 years. In Quebec, the annual number of hospitalizations for rotavirus gastroenteritis in 0-4 year olds was estimated as 2,000-2,500, representing 40-50% of the annual number of its hospitalizations for gastroenteritis in this age range within the province. Hospital-acquired rotavirus infection among children also results in significant burden, both by prolonging the affected child's hospital stay and act as a reservoir that can propagate additional cases of nosocomial rotavirus. Globally, the incidence rates of nosocomial rotavirus infection vary, ranging from 0.97 to 27.7 per 100 hospital admissions. A surveillance study conducted in the Halifax regional municipality over the period of 1991-1999 observed that rotavirus infection accounted for 31% of nosocomial diarrhea episodes with an identified pathogen in children <18 years of age. The incidence of circulating rotavirus strains documented in recent Canadian reports has indicated that the distribution of rotavirus strains identified is similar to other developed countries, with G1 as the predominant strain, with only sporadic isolations of other serotypes.

Worldwide, circulating strains of G serotypes 1 to 4, associated with P genotypes P[8] and P[4] (G1P[8], G2P[4], G3P[8], and G4P[8]) predominate. Based on a recent review of the global distribution of rotavirus serotypes/genotypes, these strains were responsible for 88.5% of rotavirus diarrhea among children worldwide, with G1P[8] type being the predominant strain accounting for 64.7% of rotavirus infections.

Based on the distribution of P and G combinations, G1P[8], G2P[4], G3P[8] and G4P[8] represent over 90% of the rotavirus infections in North America, Europe and Australia.

### **Mechanism of Action**

ROTARIX™ contains a live, attenuated human rotavirus that replicates in the small intestine and induces immunity. ROTARIX™ vaccine is derived from the human 89-12 strain which belongs to G1 serotype and P[8] genotype. G1 is the most prevalent strain worldwide. It is known that the genotype P[8] is shared by most other circulating strains, including serotypes G3, G4 and G9.

The immunologic mechanism by which ROTARIX™ protects against rotavirus gastroenteritis is not completely understood. A relationship between antibody responses to rotavirus vaccination and protection against rotavirus gastroenteritis has not been established.

## **STORAGE AND STABILITY**

Store in a refrigerator (2°C to 8°C). Do not freeze.

In order to protect the vaccine from light it is recommended that the vaccine is stored in the original package.

The expiry date of the vaccine is indicated on the label and packaging.

## **SPECIAL HANDLING INSTRUCTIONS**

The vaccine is presented as a clear, colorless liquid, free of visible particles, for oral administration.

The vaccine is ready to use (no reconstitution or dilution is required).

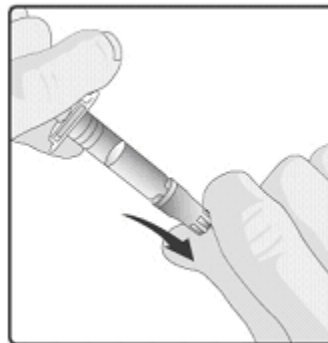
The vaccine is to be administered orally without mixing with any other vaccines or solutions.

The vaccine should also be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, discard the vaccine. Any unused vaccine or waste material should be disposed of in accordance with local requirements.

This medicinal product must not be mixed with other medicinal products.

## Administration of the vaccine

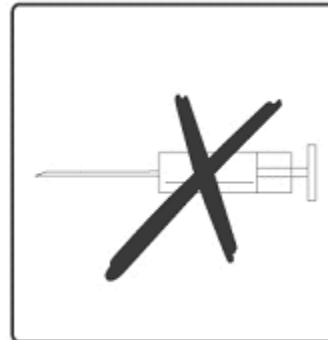
1. Remove the protective tip cap from the **oral** applicator.



2. This vaccine is for **oral administration only**. The child should be seated in a reclining position. Administer **orally** (i.e. into the child's mouth towards the inner cheek) the entire content of the **oral** applicator.



3. **Do not inject.**



## DOSAGE FORMS, COMPOSITION AND PACKAGING

### Dosage Form

ROTARIX™ vaccine is available as an oral suspension (1.5 mL).

## **Composition**

Each 1.5 mL dose is formulated to contain not less than  $10^{6.0}$  CCID<sub>50</sub> of human rotavirus RIX4414 strain (live, attenuated), produced on Vero cells. Each dose also contains Dulbecco's Modified Eagle Medium (DMEM), sucrose, di-sodium adipate and sterile water.

## **Packaging**

### **Oral Applicator**

ROTARIX™ is available in an oral applicator (Type 1, Ph. Eur.) with a plunger stopper (butyl rubber) in pack sizes of 1, 5, 10, 25, 50 or 100.

## **PART II: SCIENTIFIC INFORMATION**

### **PHARMACEUTICAL INFORMATION**

#### **Drug Substance**

Proper name: Human rotavirus, live, attenuated, oral vaccine.

#### **Product Characteristics**

ROTARIX™ (human rotavirus, live, attenuated, oral vaccine) is a monovalent, live, attenuated virus vaccine derived from the human 89-12 strain which belongs to G1 serotype and P[8] genotype. G1 is the most prevalent strain worldwide. It is known that the genotype P[8] is shared by most other circulating strains, including serotypes G3, G4 and G9. Natural infection with the virus is not limited to the G and P related antigens, but also is associated with the structural proteins VP2 and VP6, in addition to VP7 and VP4 as well as with the non-structural proteins such as NSP4. It has been shown that the induction of an immune response following vaccination with an attenuated G1P[8] human strain is sufficient to provide cross-protection against severe gastroenteritis linked to different G strains.

## CLINICAL TRIALS

- **Protective efficacy of ROTARIX™ lyophilized formulation**

Clinical studies have been conducted in Europe and Latin America to evaluate the protective efficacy of ROTARIX™ against any and severe rotavirus gastroenteritis.

**Table 5 Study demographics and trial design**

Study No.	Trial design	Dosage and route of administration	No. of subjects	Mean age at administration in weeks (range)	Gender
Rota-004	Multi-centre, double blinded, randomized, placebo controlled study	Oral 2 doses of 10 <sup>4.7</sup> foci forming units (ffu) at 2 and 4 months of age	<u>First efficacy follow-up:</u> 245 Vaccine 123 Placebo  <u>Second efficacy follow-up:</u> 241 Vaccine 120 Placebo	<u>First dose:</u> Vaccine: 8.3 (6-12) Placebo: 8.2 (6-12)  <u>Second dose:</u> Vaccine: 16.3 (10-12) Placebo: 16.1(13-22)	Vaccine: Male 53.5%  Placebo: Male: 50.4%
Rota-006	Multi-centre, multi-country, double blind, randomized, placebo controlled study	Oral 2 doses (of either 10 <sup>4.7</sup> , 10 <sup>5.2</sup> or 10 <sup>5.8</sup> foci forming units (ffu) at 2 and 4 months of age	<u>First efficacy follow-up:</u> 1,392 Vaccine 454 Placebo  <u>Second efficacy follow-up:</u> 332 Vaccine 109 Placebo	<u>First dose:</u> Vaccine*: 8.3 (6-12) Placebo: 8.3 (6-12)  <u>Second dose:</u> Vaccine: 17.9 (13-28) Placebo: 17.9 (13-26)	Vaccine & Placebo Male: 52%
Rota-023	Multi-centre, multi-country, double blinded, randomized, placebo controlled study	Oral 2 doses of 10 <sup>6.5</sup> CCID <sub>50</sub> at 2 and 3 to 4 months of age <sup>1</sup>	<u>First efficacy follow-up:</u> 9,009 Vaccine 8,858 Placebo  <u>Second efficacy follow-up:</u> 7,175 Vaccine 7,062 Placebo	<u>First dose:</u> Vaccine: 8.4 (5-13) Placebo: 8.4 (2-13)  <u>Second dose:</u> Vaccine: 16.3 (10-36) Placebo: 16.3 (9-30)	Vaccine: Male: 50.1%  Placebo: Male: 52.0%
Rota-036	Multi-centre, multi-country, double blinded, randomized, placebo controlled study	Oral 2 doses of 10 <sup>6.5</sup> CCID <sub>50</sub> at a 2, 3 months, 2, 4 months, 3, 4 months or 3, 5 months schedule <sup>1</sup>	<u>First efficacy follow-up:</u> 2,572 Vaccine 1,302 Placebo  <u>Second efficacy follow-up:</u> 2,554 Vaccine 1,294 Placebo	<u>First dose:</u> Vaccine: 11.5 (5-18) Placebo: 11.5 (6-16)  <u>Second dose:</u> Vaccine: 19.7 (10-30) Placebo: 19.7 (10-27)	Vaccine: Male 53.6 %  Placebo: Male: 50.9%

Note: The administration schedule depends on the countries in which the studies were conducted.

\* This is applicable to the 10<sup>5.8</sup> ffu titre vaccine

Clinical studies on protective efficacy were undertaken with ROTARIX™ lyophilized formulation, on which ROTARIX™ approval was based. Subsequently, clinical studies were undertaken with the liquid formulation to assess the elicited immune response compared to the lyophilized formulation, including a non-inferiority study (see Protective efficacy of ROTARIX™ liquid formulation).

## Results

A clinical study performed in Europe (Rota-036) evaluated ROTARIX™ given according to different European schedules (2, 3 months; 2, 4 months; 3, 4 months; 3, 5 months) in more than 3,800 subjects. Severity of gastroenteritis was defined according to the Vesikari 20-point scale which evaluates the full clinical picture of rotavirus gastroenteritis by taking into account the severity and duration of diarrhea and vomiting, the severity of fever and dehydration as well as the need for treatment.

## Safety

For safety information refer to the Adverse Reactions section, Part 1

## Efficacy

**Table 6 Efficacy following two doses of ROTARIX™ persisting through the first and second rotavirus seasons**

	1 <sup>st</sup> Rotavirus Season		2 <sup>nd</sup> Rotavirus Season	
	Efficacy (%)	95% CI	Efficacy (%)	95% CI
Any rotavirus gastroenteritis	87.1*	79.6;92.1	71.9*	61.2;79.8
Severe rotavirus gastroenteritis (Vesikari score $\geq$ 11)	95.8*	89.6;98.7	85.6*	75.8;91.9
Rotavirus gastroenteritis requiring medical attention	91.8*	84;96.3	76.2*	63.0;85.0
Hospitalization due to rotavirus gastroenteritis	100*	81.8;100	92.2*	65.6;99.1

\* Statistically significant ( $p < 0.05$ )

Vaccine efficacy during the first year of life progressively increased with increasing disease severity, reaching 100% (95% CI: 84.7;100) for Vesikari scores  $\geq$ 17.

**Table 7 Efficacy was evaluated in 2,572<sup>†</sup> ROTARIX™ vaccines and 1,302<sup>†</sup> placebo recipients through 2 rotavirus seasons (Rota-036)**

Type	Through One Rotavirus Season				Through Two Rotavirus Seasons			
	Rotavirus gastroenteritis of any severity		Severe rotavirus <sup>^</sup> gastroenteritis		Rotavirus gastroenteritis of any severity		Severe rotavirus <sup>^</sup> gastroenteritis	
	Efficacy (%)	95% CI	Efficacy (%)	95% CI	Efficacy (%)	95% CI	Efficacy (%)	95% CI
G1[P8]	95.6*	87.9;98.8	96.4*	85.7;99.6	89.8*	82.9;94.2	96.4*	90.4;99.1
G2P[4]	62.0	-124.4;94.4	74.7	-386.2;99.6	58.3*	10.1;81.0	85.5*	24.0;98.5
G3[P8]	89.9*	9.5;99.8	100.0*	44.8;100.0	84.8*	41.0;97.3	93.7*	52.8;99.9
G4[P8]	88.3*	57.5;97.9	100.0*	64.9;100.0	83.1*	55.6;94.5	95.4*	68.3;99.9
G9[P8]	75.6*	51.1;88.5	94.7*	77.9;99.4	72.9*	59.3;82.2	85.0*	71.7;92.6
Strains with [P8] genotype	88.2*	80.8;93.0	96.5*	90.6;99.1	n.a	n.a	n.a	n.a
Pooled non G1 (G2, G3, G4, G9, G12)	n.a	n.a	n.a	n.a	72.9*	62.9; 80.5	87.7*	78.9; 93.2

<sup>†</sup>ATP cohort for efficacy

\* Statistically significant (p< 0.05)

<sup>^</sup> Severe gastroenteritis defined as a score ≥ 11 on the Vesikari scale.

A clinical study performed in Latin America (Rota-023) evaluated ROTARIX™ in more than 17,500 subjects. Severity of gastroenteritis was defined according to WHO criteria. The protective vaccine efficacy against severe rotavirus gastroenteritis requiring hospitalization and/or rehydration therapy in a medical facility and the type specific vaccine efficacy after 2 doses of ROTARIX™ are presented in the Table 8A below:

Due to the rareness of the G2P[4] serotype, a meta analysis was performed. A pooled analysis of four efficacy studies, listed in Table 5, showed a 71.4% (95% CI:20.1;91.1) efficacy against severe rotavirus gastroenteritis (Vesikari score ≥11) caused by rotavirus G2P[4] type during the first year of life. Please see Table 8B below:

**Table 8A Type specific vaccine efficacy following 2 doses of ROTARIX™ (Rota-023)**

Type	Severe rotavirus gastroenteritis (1 <sup>st</sup> year of life) ROTARIX™ N=8,858; Placebo N=9,009		Severe rotavirus gastroenteritis (2 <sup>nd</sup> year of life) ROTARIX™ N=7,175; Placebo N=7,062	
	Efficacy (%)	95% CI	Efficacy (%)	95% CI
All rotavirus gastroenteritis	84.7*	71.7;92.4	79.0*	66.4;87.4
G1P[8]	91.8*	74.1;98.4	72.4*	34.5;89.9
G2P[4]	41.0	-79.2; 82.4	1.6	-7,626.1;98.6
G3P[8]	87.7*	8.3;99.7	71.9	-47.7;97.1
G4P[8]	50.8 <sup>#</sup>	-844;99.2	63.1*	0.7;88.2
G9P[8]	90.6*	61.7;98.9	87.7*	72.9;95.3
Strains with P[8] genotype	90.9*	79.2;96.8	79.5*	67.0;87.9

N=ATP cohort for efficacy

\*statistically significant (p<0.05)

<sup>#</sup> The numbers of cases on which the estimates of efficacy against G4P[8] were based were very small (1 case in the ROTARIX™ group and 2 cases in the placebo).

**Table 8B Pooled analysis of sever RV GE (score greater than or equal to 11 on Vesikari scale) due to G2P[4] type and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first year follow-up (studies Rota-004, Rota-006, Rota-023, and Rota-036, ATP cohort for efficacy)**

Study	HRV			Placebo			VE	
	N	n	%	N	n	%	%	95% CI
<b>Rota-004</b>	245	0	0.0	123	1	0.8	100.0	-1858.0;100.0
<b>Rota-006</b>	1,392	0	0.0	454	3	0.7	100.0	21.1;100.0
<b>Rota-023</b>	9,009	5	0.1	8,858	9	0.1	45.4	-81.5;85.6
<b>Rota-036</b>	2,572	1	0.0	1,302	2	0.2	64.7	-386.2;99.57
<b>All*</b>	1,3218	6	0.0	10,737	15	0.1	71.4	20.1;91.1

Results from the first efficacy follow-up period on the ATP cohort for efficacy

\*VE defined as 1-stratified Poisson rate ratio

## Immune response

The immunologic mechanism by which ROTARIX™ protects against rotavirus gastroenteritis is not completely understood. A relationship between antibody responses to rotavirus vaccination and protection against rotavirus gastroenteritis has not been established. The following table shows the percentage of infants with serum anti-rotavirus IgA antibody titres  $\geq 20$  U/ml (by ELISA) one to two months after the second dose of vaccine or placebo as observed in different studies.

**Table 9** Percent of infants with serum anti-rotavirus IgA antibody titres  $\geq 20$  U/mL 1 to 2 months after the second dose

Schedule	Studies conducted in	Vaccine			Placebo		
		N	% $\geq 20$ U/mL	95% CI	N	% $\geq 20$ U/mL	95% CI
<b>2, 3 months</b>	France, Germany	239	82.8	77.5;87.4	127	8.7	4.4;15.0
<b>2, 4 months</b>	Spain	186	85.5	79.6;90.2	89	12.4	6.3;21.0
<b>3, 5 months</b>	Finland, Italy	180	94.4	90.0;97.3	114	3.5	1.0;8.7
<b>3, 4 months</b>	Czech Republic	182	84.6	78.5;89.5	90	2.2	0.3;7.8
<b>2, 3 to 4 months</b>	Latin America; 11 countries	393	77.9	73.8;81.6	341	15.1	11.7;19.0

### Immune Response in Preterm Infants

In a clinical study conducted in preterm infants, ROTARIX™ was immunogenic; 85.7% of subjects achieved serum anti-rotavirus IgA antibody titres  $\geq 20$  U/mL (by ELISA) one month after the second dose of the vaccine.

- **Protective efficacy of ROTARIX™ liquid formulation**

Four controlled studies were undertaken with ROTARIX™ liquid formulation to assess elicited immune response. Three of these were comparative studies in which healthy infants were enrolled to receive two doses of ROTARIX™ liquid or lyophilized formulations, given at the age of 2 and 3 months (Rota-048), 2 and 4 months (Rota-057), or 3 and 4 months (Rota-061). The immune response elicited by ROTARIX™ liquid formulation was comparable to that elicited by the lyophilized formulation (Table 10).

**Table 10** Percent of infants with serum anti-rotavirus IgA antibody titres  $\geq 20$ U/mL 1 month after the second dose

Schedule	Studies conducted in	Liquid Formulation			Lyophilized Formulation		
		N	% $\geq 20$ U/mL	95% CI	N	% $\geq 20$ U/mL	95% CI
<b>2, 3 months</b>	Finland	80	90.0	81.2;95.6	86	83.7	74.2;90.8
<b>2, 4 months</b>	Panama	449	80.8	76.9;84.4	434	73.5	69.1;77.6
<b>3, 4 months</b>	Finland	746	88.6	86.1;90.8	252	90.5	86.2;93.8

In a study conducted in Vietnam (Rota-051), the immune response in terms of seroconversion rates and GMCs in the group that received two doses of ROTARIX™ liquid vaccine with the first and second dose given at 8 and 12 weeks of age (4 weeks apart) was lower than the response in the group that received two doses of ROTARIX™ liquid vaccine with the first and second dose given at 8 and 16 weeks of age (8 weeks apart).

Serum anti-RV IgA antibodies are generally accepted as a valid surrogate marker of protection, and published data suggests that the ROTARIX™-induced serum anti-RV IgA antibodies might be a good correlate of vaccine induced protection, despite the absence of an established immune correlate of protection. The immune response observed after two doses of ROTARIX™ liquid formulation was comparable to the immune response observed after 2 doses of ROTARIX™ lyophilized formulation, the vaccine efficacy for the liquid formulation is assumed to be similar to that observed with the lyophilized formulation.

## **TOXICOLOGY**

Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity.

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**PART III: CONSUMER INFORMATION****ROTARIX™**

Human rotavirus, live, attenuated oral vaccine

This leaflet is part III of a three-part "Product Monograph" published when ROTARIX™ (human rotavirus, live, attenuated oral vaccine) was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about ROTARIX™. Contact your doctor or pharmacist if you have any questions about the vaccine.

**ABOUT THIS VACCINE****What the vaccine is used for:**

ROTARIX™ is a viral vaccine, containing live, attenuated human rotavirus, that helps to protect your child against gastroenteritis (diarrhea and vomiting) caused by rotavirus infection.

Rotavirus infection is the most common cause of severe diarrhea in infants and young children. Rotavirus is easily spread from hand-to-mouth due to contact with stools from an infected person. Most children with rotavirus diarrhea recover on their own. However, some children become very ill with severe vomiting, diarrhea and life-threatening loss of fluids that requires hospitalization. Rotavirus infections are responsible for hundreds of thousands of deaths worldwide every year especially in developing countries, where nutrition and health care are not optimal.

When a person is given the vaccine, the immune system (the body's natural defences) will make antibodies against the most commonly occurring types of rotavirus. These antibodies protect against disease caused by these types of rotavirus.

As with all vaccines, ROTARIX™ may not completely protect all people who are vaccinated against the rotavirus infections. It is intended to prevent.

**What it does:**

When your child receives this vaccine, his/her immune system (the body's natural defence) will make antibodies that will recognize the most commonly occurring types of rotavirus. These antibodies protect against disease caused by these types of rotavirus and will protect your child from infection.

**When it should not be used:**

Please see WARNINGS AND PRECAUTIONS section.

**Take special care with ROTARIX™:**

Excretion of the live vaccine virus in the stools of vaccinated children is known to occur after vaccination, especially around the 7th day. Persons in contact with recent vaccinated children should wash their hands after changing the child's diapers.

ROTARIX™ should be given with caution to children in close contact with individuals having any disease or receiving any medicine which may reduce his/her resistance to infection.

**What the medicinal ingredient is:**

ROTARIX™ consists of live, attenuated human rotavirus.

**What the important nonmedicinal ingredients are:**

The important nonmedical ingredients are Dulbecco's Modified Eagle Medium (DMEM), sucrose, di-sodium adipate, and sterile water.

**What dosage forms it comes in:**

The ROTARIX™ vaccine is a suspension for oral administration.

ROTARIX™ is supplied as a suspension in a single dose oral applicator.

**WARNINGS AND PRECAUTIONS**

BEFORE you use ROTARIX™ talk to your doctor or pharmacist if your child:

- has previously had any allergic reaction to rotavirus vaccines or any component contained in ROTARIX™ (the active substances and other ingredients in ROTARIX™; see What the medicinal ingredient is and What the important nonmedicinal ingredients are sections). Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.
- has an intolerance to some sugars (See What the important nonmedicinal ingredients are).
- was born with a malformation of the gastrointestinal system that would predispose for intussusception.
- has any disease or is taking any medicine which reduces his/her resistance to infection.
- has a severe infection with a high temperature. It might be necessary to postpone the vaccination until recovery. A minor infection such as a cold should not be a problem, but talk to your doctor first.
- has diarrhea or is vomiting. It might be necessary to postpone the vaccination until recovery.

## INTERACTIONS WITH THIS VACCINE

Please tell your doctor if your child is taking or has recently taken any other medicines, including medicines obtained without a prescription, or has recently received any other vaccine.

ROTARIX™ may be given at the same time your child receives other normally recommended vaccinations, such as diphtheria, tetanus, pertussis (whooping cough), *Haemophilus influenzae* type b, inactivated polio, hepatitis B, pneumococcal vaccines as well as meningococcal serogroup C conjugate vaccine.

## PROPER USE OF THIS VACCINE

### Usual dose:

The Health Care provider will administer the recommended dose of ROTARIX™ to your child. The vaccine (1.5 mL liquid) will be given orally. **Under no circumstance should this vaccine be administered by injection.**

Your child will receive two doses of the vaccine. Each dose will be given on a separate occasion with an interval of at least 4 weeks between the two doses. The first dose may be given from the age of 6 weeks. The two doses of the vaccine must have been given by the age of 24 weeks, although they should preferably have been given before 16 weeks of age.

ROTARIX™ may be given to infants who were born prematurely following the same vaccination course.

Your doctor may suggest giving the ROTARIX™ vaccine during the 2 and 4 month visits when getting some of the other vaccines.

In case your child spits out or regurgitates most of the vaccine dose, a single replacement dose may be given at the same vaccination visit.

There are no restrictions on the infant's consumption of food or liquid, including breastmilk, either before or after the vaccination.

When ROTARIX™ is given to your child for the first dose, it is recommended that your child also receives ROTARIX™ (and not another rotavirus vaccine) for the second dose.

### Missed Dose:

It is important that you follow the instructions of your Health Care Provider regarding return visits. If you forget to go back to your doctor at the scheduled time, ask your doctor for advice.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, ROTARIX™ can cause side effects, although not everybody gets them. Side effects that occurred during clinical trials with ROTARIX™ were as follows:

Very common (side effects which may occur in more than 10% of doses):

- loss of appetite
- irritability

Common (side effects which may occur between 1% and 10% of doses):

- fever, fatigue
- diarrhea, vomiting, or regurgitation of food, flatulence and abdominal pain.

Uncommon (side effects which may occur between 0.1% and 1% of doses):

- sleep disorder, sleepiness
- constipation

Rare (side effects which may occur between 0.01% and 0.1% of doses):

- upper respiratory tract infections, hoarseness, runny nose
- dermatitis, rash
- muscle cramp

*This is not a complete list of side effects. For any unexpected effects while taking ROTARIX™, contact your doctor or pharmacist.*

## HOW TO STORE IT

- Keep out of reach and sight of children.
- Store in a refrigerator (2°C to 8°C).
- Do not freeze.
- Store in original package to protect from light.

**REPORTING SUSPECTED SIDE EFFECTS**

To monitor vaccine safety, the Public Health Agency of Canada collects information on serious and unexpected adverse events following vaccination. If you suspect you have had a serious or unexpected event following receipt of a vaccine you may notify the Public Health Agency of Canada:

By toll-free telephone: 1-866-844-0018  
By toll-free fax: 1-866-844-5931  
Web Address: <http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php>

By regular mail:  
Vaccine Safety  
130 Colonnade Road  
Ottawa, Ontario  
K1A 0K9 Address Locator 6502A

**NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.**

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.gsk.ca>

or by contacting the sponsor, GlaxoSmithKline Inc.  
7333 Mississauga Road  
Mississauga, Ontario  
L5N 6L4  
1-800-387-7374

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