Rotarix

Rotavirus vaccine

Oral suspension

QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (1.5 ml) contains:
Live attenuated human rotavirus RIX4414 strain* of the G1P[8] type: not less than $10^{6.0}$ $CCID_{50}$

*Produced on Vero cells

The vaccine is a clear and colourless liquid.

CLINICAL INFORMATION

Indications

Rotarix is indicated for the active immunisation of infants from the age of 6 weeks for prevention of gastro-enteritis due to rotavirus infection (*see sections Dosage and Administration, Warnings and Precautions, and Pharmacodynamics*).

Dosage and Administration

Posology
The vaccination course consists of two doses. The first dose may be administered from the age of 6 weeks. There should be an interval of at least 4 weeks between doses. The vaccination course should preferably be given before 16 weeks of age, but must be completed by the age of 24 weeks.

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.

It is 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.

Method of administration
Rotarix is for **oral** use only. Administer the entire content (1.5 ml) of the **oral** applicator **ORALLY** on the inside of the cheek.

ROTARIX SHOULD UNDER NO CIRCUMSTANCES BE INJECTED.

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

Based on evidence generated in clinical trials, breast-feeding does not reduce the protection against rotavirus gastro-enteritis afforded by ***Rotarix***. Therefore, breast-feeding may be continued during the vaccination schedule.

For information on instructions for administration, see section *Use and Handling*.

Contraindications

Rotarix should not be administered to subjects who have on-going diarrhoea or vomiting.

Rotarix should not be administered to subjects with known hypersensitivity after previous administration of ***Rotarix*** vaccine or to any component of the vaccine (*see sections Qualitative and Quantitative Composition and List of Excipients*).

Subjects with history of intussusception.

Subjects with uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose to intussusception.

Rotarix should not be administered to subjects with known or suspected immune deficiency diseases and conditions such as combined immunodeficiency, hypogammaglobulinemia, agammaglobulinemia, human immunodeficiency virus (HIV) infection, thymic abnormalities, malignancy, leukemia, lymphoma, or advanced debilitating conditions.

Rotarix should not be administered to subjects who may be immunosuppressed or have an altered or compromised immune status, such as those who are being treated with systemic corticosteroids, alkylating drugs, antimetabolites, radiation, or other immunosuppressive therapies.

Subjects with Severe Combined Immunodeficiency (SCID) disorder *(see section Adverse Reactions)*.

Warnings and Precautions

Prior to administration of this vaccine, healthcare personnel should inform the parent or guardian of the benefits and risks to the vaccinee, and the importance of completing the immunisation series. Parents or guardians should be instructed to report any serious adverse reactions to their health care provider.

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 subjects suffering from acute severe febrile illness (>38.5ºC). However, the presence of a minor infection, such as cold, should not result in the deferral of vaccination.

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.

The risk of intussusception has been evaluated in a large safety trial (including 63,225 infants) conducted in Latin America and Finland. No increased risk of intussusception was observed in this clinical trial following administration of ***Rotarix*** when compared with placebo (*see section Adverse Reactions*).

However, post-marketing safety studies indicate a transient increased incidence of intussusception after vaccination, mostly within 7 days of the first dose and, to a lesser extent, the second dose. The overall incidence of intussusception remains rare. Whether ***Rotarix*** affects the overall risk of intussusception has not been established.

As a precaution, healthcare professionals should follow-up on any symptoms indicative of intussusception (severe abdominal pain, persistent vomiting, bloody stools, abdominal bloating and/or high fever). Parents/guardians should be advised to promptly report such symptoms.

For subjects with a predisposition for intussusception, *see Contraindications*.

Administration of ***Rotarix*** in immunosuppressed infants, including infants on immunosuppressive therapy, should be based on careful consideration of potential benefits and risks (*see section Pharmacodynamics*).

Excretion of the vaccine virus in the stools is known to occur after vaccination and lasts for 10 days on average with peak excretion around the 7th day. In clinical trials, cases of transmission of excreted vaccine virus to seronegative contacts of vaccinees have been observed without causing any clinical symptoms. ***Rotarix*** should be administered with caution to individuals with immunodeficient close contacts, such as individuals with malignancies, or who are otherwise immunocompromised or receiving immunosuppressive therapy. Contacts of recent vaccinees should be advised to observe careful hygiene (including washing their hands) when changing children's nappies.

Information is not available regarding the administration of ***Rotarix*** to individuals who had recently received immune globulin-containing products either orally or parenterally.

Limited data in 140 premature children indicate that ***Rotarix*** can be given to premature children, however the level of clinical protection remains unknown.

As with any vaccine, a protective immune response may not be elicited in all vaccinees (*see section Pharmacodynamics*).

The extent of protection that ***Rotarix*** might provide against rotavirus strains that have not been circulating in clinical trials is currently unknown (*see section Pharmacodynamics*).

Rotarix does not protect against gastro-enteritis due to other pathogens than rotavirus.

ROTARIX SHOULD UNDER NO CIRCUMSTANCES BE INJECTED.

Interactions

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. Although concomitant administration of OPV may slightly reduce the immune response to rotavirus vaccine, clinical protection against severe rotavirus gastro-enteritis was shown to be maintained in a clinical trial involving more than 4,200 subjects who received ***Rotarix*** concomitantly with OPV.

Antibodies to rotavirus may be detected in breast milk. Based on evidence generated in clinical trials, breast-feeding does not reduce the protection against rotavirus gastro-enteritis afforded by ***Rotarix***. Therefore, breast-feeding may be continued during the vaccination schedule.

Pregnancy and Lactation

Rotarix is not intended for use in adults. Thus, human data on use during pregnancy or lactation are not available and animal reproduction studies have not been performed.

Effects on Ability to Drive and Use Machines

Rotarix is not intended for use in adults.

Adverse Reactions

Clinical trial data
The following convention has been used for the classification of frequency:

Very common	≥1/10
Common	≥1/100 and <1/10
Uncommon	≥1/1,000 and <1/100
Rare	≥1/10,000 and <1/1,000
Very rare	<1/10,000

The safety profile presented below is based on data from clinical trials conducted with either the lyophilised or the liquid formulation of ***Rotarix***.

In a total of four clinical trials, approximately 3,800 doses of ***Rotarix*** liquid formulation were administered to approximately 1,900 infants. Those trials have shown that the safety profile of the liquid formulation is comparable to the lyophilised formulation.

In a total of twenty-three clinical trials, approximately 106,000 doses of ***Rotarix*** (lyophilised or liquid formulation) were administered to approximately 51,000 infants.

In three placebo-controlled clinical trials, in which ***Rotarix*** was administered alone (administration of routine paediatric vaccines was staggered), the incidence and severity of the solicited events (collected 8 days post-vaccination), diarrhoea, vomiting, loss of appetite, fever, irritability and cough/runny nose, were not significantly different in the group receiving ***Rotarix*** when compared to the group receiving placebo. No increase in the incidence or severity of these events was seen with the second dose.

In a pooled analysis from seventeen placebo-controlled clinical trials including trials in which ***Rotarix*** was co-administered with routine paediatric vaccines (*see section Interactions*), the following adverse reactions (collected 31 days post-vaccination) were considered as possibly related to vaccination.

Gastrointestinal disorders
Common: diarrhoea
Uncommon: flatulence, abdominal pain

Skin and subcutaneous tissue disorders
Uncommon: dermatitis

General disorders and administration site conditions
Common: irritability

The risk of intussusception has been evaluated in a large safety trial conducted in Latin America and Finland where 63,225 subjects were enrolled. This trial gave evidence of no increased risk of intussusception in the ***Rotarix*** group when compared with the placebo group as shown in the table below.

	Rotarix	**Placebo**	**Relative risk (95% CI)**
Intussusception within 31 days after administration of:	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)
Intussusception up to one year of age:	N=10,159	N=10,010	
First dose up to one year of age	4	14	0.28 (0.10;0.81)

CI: confidence interval

Parents and caretakers should be advised to contact their doctors urgently if the vaccinated child develops any or all features of intussusception (abdominal bloating or severe colicky pain, bloody or black stools, or persistent vomiting). Doctors should consider this diagnosis in children with these symptoms.

Safety in preterm infants
In a clinical study, 1,009 preterm infants were administered ***Rotarix*** lyophilised formulation 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. Serious adverse events were observed in 5.1% of recipients of ***Rotarix*** as compared to 6.8% of placebo recipients. Similar rates of other adverse events were observed in ***Rotarix*** and placebo recipients. No cases of intussusception were reported.

Post-marketing data
Gastrointestinal disorders
Rare: haematochezia, gastro-enteritis with vaccine viral shedding in infants with Severe Combined Immunodeficiency (SCID) disorder.
Very rare: intussusception (*see section Warnings and Precautions*).

Overdose

Some cases of overdose have been reported. In general, the adverse event profile reported in these cases was similar to that observed after administration of the recommended dose of ***Rotarix***.

PHARMACOLOGICAL PROPERTIES

Pharmaco-therapeutic group: viral vaccines, ATC code: J07BH01

Pharmacodynamics

Protective efficacy

In clinical trials, efficacy was demonstrated against gastro-enteritis due to rotavirus of the most common genotypes G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8]. In addition, efficacy against uncommon rotavirus genotypes G8P[4](severe gastro-enteritis) and G12P[6] (any gastro-enteritis) has been demonstrated. These strains are circulating worldwide.

Clinical studies have been conducted in Europe, Latin America, Africa and Asia to evaluate the protective efficacy of ***Rotarix*** against any and severe rotavirus gastro-enteritis.

Severity of gastro-enteritis was defined according to two different criteria:
- the Vesikari 20-point scale, which evaluates the full clinical picture of rotavirus gastro-enteritis by taking into account the severity and duration of diarrhoea and vomiting, the severity of fever and dehydration as well as the need for treatment;
or
- the clinical case definition based on World Health Organization (WHO) criteria.

Protective efficacy in Europe
A clinical study performed in Europe evaluated ***Rotarix*** given according to different European schedules (2, 3 months; 2, 4 months; 3, 4 months; 3, 5 months) in 4,000 subjects. Severity of gastro-enteritis was defined according to the Vesikari 20-point scale which evaluates the full clinical picture of rotavirus gastro-enteritis by taking into account the severity and duration of diarrhoea and vomiting, the severity of fever and dehydration as well as the need for treatment.

After two doses of ***Rotarix***, the protective vaccine efficacy observed during the first and second year of life is presented in the following table:

	1st year of life ***Rotarix* N=2,572;**	**2nd year of life** ***Rotarix* N=2,554;**

	Placebo N=1,302 (§)		Placebo N=1,294 (§)	
Vaccine efficacy (%) against any and severe rotavirus gastro-enteritis [95% CI]				
Strain	**Any severity**	**Severe†**	**Any severity**	**Severe†**
G1P[8]	95.6 [87.9;98.8]	96.4 [85.7;99.6]	82.7 [67.8;91.3]	96.5 [86.2;99.6]
G2P[4]	62.0* [<0.0;94.4]	74.7* [<0.0;99.6]	57.1 [<0.0;82.6]	89.9 [9.4;99.8]
G3P[8]	89.9 [9.5;99.8]	100 [44.8;100]	79.7 [<0.0;98.1]	83.1* [<0.0;99.7]
G4P[8]	88.3 [57.5;97.9]	100 [64.9;100]	69.6* [<0.0;95.3]	87.3 [<0.0;99.7]
G9P[8]	75.6 [51.1;88.5]	94.7 [77.9;99.4]	70.5 [50.7;82.8]	76.8 [50.8;89.7]
Strains with P[8] genotype	88.2 [80.8;93.0]	96.5 [90.6;99.1]	75.7 [65.0;83.4]	87.5 [77.8;93.4]
Circulating rotavirus strains	87.1 [79.6;92.1]	95.8 [89.6;98.7]	71.9 [61.2;79.8]	85.6 [75.8;91.9]
Vaccine efficacy (%) against rotavirus gastro-enteritis requiring medical attention [95% CI]				
Circulating rotavirus strains	91.8 [84;96.3]		76.2 [63.0;85.0]	
Vaccine efficacy (%) against hospitalisation due to rotavirus gastro-enteritis [95% CI]				
Circulating rotavirus strains	100 [81.8;100]		92.2 [65.6;99.1]	

† Severe gastro-enteritis defined as a score ≥11 on the Vesikari scale
(§) ATP cohort for efficacy
* Not statistically significant ($p \geq 0.05$). These data should be interpreted with caution.

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

Protective efficacy in Latin America

A clinical study performed in Latin America evaluated ***Rotarix*** in more than 20,000 subjects. Severity of gastro-enteritis was defined according to WHO criteria. The protective vaccine efficacy against severe rotavirus gastro-enteritis requiring hospitalisation and/or rehydration therapy in a medical facility and the strain specific vaccine efficacy after two doses of ***Rotarix*** are presented in the table below:

Strain	**Severe rotavirus gastro-enteritis† (1st year of life)** ***Rotarix*** **N=9,009; Placebo N=8,858** (§)	**Severe rotavirus gastro-enteritis† (2nd year of life)** ***Rotarix*** **N=7,175; Placebo N=7,062** (§)
	Efficacy (%) [95% CI]	**Efficacy (%) [95% CI]**
All RVGE	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]
G3P[8]	87.7 [8.3;99.7]	71.9* [<0.0;97.1]
G4P[8]	50.8#* [<0.0;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]

†Severe rotavirus gastro-enteritis was defined as an episode of diarrhoea with or without vomiting that required hospitalization and/or re-hydration therapy in a medical facility (WHO criteria)
(§) ATP cohort for efficacy
* Not statistically significant ($p \geq 0.05$). These data should be interpreted with caution.
# 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 group).

A pooled analysis of five efficacy studies*, showed a 71.4% (95% CI: 20.1;91.1) efficacy against severe rotavirus gastro-enteritis (Vesikari score ≥11) caused by rotavirus G2P[4] strain during the first year of life.
* In these studies, the doses of ***Rotarix*** used ranged from $10^{5.3}$ to $10^{6.6}$ $CCID_{50}$, and the point estimates and confidence intervals were respectively: 100% (95% CI: -1858.0; 100), 100% (95% CI: 21.1;100), 45.4% (95% CI: -81.5;86.6), 74.7 (95% CI: -386.2;99.6). No point estimate was available for the remaining study.

Protective efficacy in Africa
A clinical study performed in Africa in more than 4,900 subjects evaluated ***Rotarix*** given at approximately 10 and 14 weeks of age (2 doses) or 6, 10 and 14 weeks of age (3 doses). The vaccine efficacy against severe rotavirus gastro-enteritis during the first year of life was 61.2% (95% CI: 44.0;73.2). The study was not powered to evaluate a difference in vaccine efficacy between the 2- and 3-dose regimens.

The protective vaccine efficacy observed against any and severe rotavirus gastro-enteritis is presented in the table below.

Study conducted in Africa: 1st year of life – pooled results (*Rotarix* N=2,974; Placebo N=1,443 (§))		
Vaccine efficacy (%) against any and severe rotavirus gastro-enteritis [95% CI]		
Strain	**Any severity**	**Severe†**
G1P[8]	68.3 (53.6;78.5)	56.6 (11.8;78.8)
G2P[4]	49.3 (4.6;73.0)	83.8 (9.6;98.4)
G3P[8]	43.4* (<0;83.7)	51.5* (<0;96.5)
G8P[4]	38.7* (<0;67.8)	63.6 (5.9;86.5)

G9P[8]	41.8* (<0;72.3)	56.9* (<0;85.5)
G12P[6]	48.0 (9.7;70.0)	55.5* (<0; 82.2)
Strains with P[4] genotype	39.3 (7.7;59.9)	70.9 (37.5;87.0)
Strains with P[6] genotype	46.6 (9.4;68.4)	55.2* (<0;81.3)
Strains with P[8] genotype	61.0 (47.3;71.2)	59.1 (32.8;75.3)

† Severe gastro-enteritis was defined as a score ≥11 on the Vesikari scale
(§) ATP cohort for efficacy. This includes all subjects from the ATP cohort for safety who have entered into the concerned efficacy follow-up period.
* Not statistically significant (p ≥ 0.05). These data should be interpreted with caution.

Protective efficacy in Asia

Sustained efficacy up to 3 years of age in Asia

A clinical study conducted in Asia (Hong Kong, Singapore and Taiwan) in more than 10,000 subjects evaluated ***Rotarix*** given according to different schedules (2, 4 months of age; 3, 4 months of age). Severity of gastro-enteritis was defined according to the Vesikari 20-point scale. After two doses of ***Rotarix***, the protective vaccine efficacy observed up to 3 years of age is shown below.

	Efficacy up to 2 years of age ***Rotarix* N=5,263** **Placebo N=5,256(§)**	**Efficacy up to 3 years of age** ***Rotarix* N=5,263** **Placebo N=5,256(§)**
Vaccine efficacy (%) against severe rotavirus gastro-enteritis (95% CI)		
Strain	**Severe†**	**Severe†**
G1P[8]	100.0 (80.8;100.0)	100.0 (84.8;100.0)
G2P[4]	100.0* (<0;100.0)	100.0* (<0;100.0)
G3P[8]	94.5 (64.9;99.9)	95.2 (70.4;99.9)
G9P[8]	91.7 (43.8;99.8)	91.7 (43.8;99.8)
Strains with P[8] genotype	95.8 (83.8;99.5)	96.6 (87.0;99.6)
Circulating rotavirus strains	96.1 (85.1;99.5)	96.9 (88.3;99.6)
Vaccine efficacy (%) against rotavirus gastro-enteritis requiring hospitalisation and/or rehydration therapy in a medical facility [95% CI]		
Circulating rotavirus strains	94.2 (82.2;98.8)	95.5 (86.4;99.1)

† Severe gastro-enteritis was defined as a score ≥11 on the Vesikari scale

(§) ATP cohort for efficacy. This includes all subjects from the ATP cohort for safety who have entered into the concerned efficacy follow-up period.
* Not statistically significant ($p \geq 0.05$). These data should be interpreted with caution.

Protective efficacy of the liquid formulation

Since the immune response observed after 2 doses of ***Rotarix*** liquid formulation was comparable to the immune response observed after 2 doses of ***Rotarix*** lyophilised formulation, the levels of vaccine efficacy observed with the lyophilised formulation can be extrapolated to the liquid formulation.

Immune response

The immunologic mechanism by which ***Rotarix*** protects against rotavirus gastro-enteritis is not completely understood. A relationship between antibody responses to rotavirus vaccination and protection against rotavirus gastro-enteritis has not been established.

The following table shows the percentage of subjects initially seronegative for rotavirus (IgA antibody titres <20U/ml (by ELISA)) and with serum anti-rotavirus IgA antibody titers ≥20U/ml one to two months after the second dose of vaccine or placebo as observed in different studies with ***Rotarix*** lyophilised formulation.

Schedule	**Studies conducted in Europe**	**Vaccine (N=794)**	**Placebo (N=422)**
2, 3 months	France	84.3%	14.0%
	Germany	82.1%	6.0%
2, 4 months	Spain	85.5%	12.4%
3, 5 months	Finland	94.6%	2.9%
	Italy	92.3%	11.1%
3, 4 months	Czech Republic	84.6%	2.2%
Schedule	**Studies conducted in Latin America**	**Vaccine (N=1,023)**	**Placebo (N=448)**
2, 3 to 4 months	11 countries	77.9%	15.1%
2, 4 months	3 countries	85.5%	17.1%
Schedule	**Studies conducted in Asia**	**Vaccine (N=140)**	**Placebo (N=136)**
2, 4 months	Taiwan	100%	4.5%
	Hong Kong	95.2%	0.0%
3, 4 months	Singapore	97.8%	2.1%
Schedule	**Study conducted in Africa**	**Vaccine (N=221)**	**Placebo (N=111)**
10, 14 weeks and 6, 10, 14 weeks (Pooled)	South Africa, Malawi	58.4%	22.5%

In three comparative controlled trials, the immune response elicited by ***Rotarix*** liquid formulation was comparable to the one elicited by ***Rotarix*** lyophilised formulation.

Data are insufficient to establish the safety and efficacy of ***Rotarix*** in premature infants less than 37 weeks gestation. Moreover, it is not known whether premature infants are at higher risk for rotavirus hospitalisation when compared with full-term infants. Until such data become available, physicians should individually weigh the potential benefits and risks of administering ***Rotarix*** to a premature infant.

Rotarix does not protect against non-rotaviral gastro-enteritis, or against diarrhoea due to other infectious and non-infectious causes.

Effectiveness

In observational studies, vaccine effectiveness was demonstrated against severe gastro-enteritis leading to hospitalisation due to rotavirus of common genotypes G1P[8], G2P[4], G3P[8] and G9P[8] as well as the less common rotavirus genotype G9P[4] and G9P[6]. All of these strains are circulating worldwide.

Below table shows the results of several matched case-control studies conducted to evaluate the effectiveness of ***Rotarix*** against severe rotavirus gastro-enteritis leading to hospitalisation.

Effectiveness against severe rotavirus gastro-enteritis leading to hospitalisation:

Countries	**Age**	**N$ (cases/ controls)**	**Effectiveness after 2 doses RV hospitalisation**	
			Strain	**Effectiveness (%) [95% CI]**
High Income Countries				
Belgium	< 4 yrs	160/198	All G1P[8] G2P[4]	90 [81;95] 95 [78;99] 85 [64;94]
	3-11 m		All G2P[4]	91 [75;97] 83 [22;96]±
Singapore	< 5 yrs	136/272	All G1P[8]	84 [32;96] 91 [30;99]
Taiwan	< 3 yrs	184/1,623†	All G1P[8]	92 [75;98] 95 [69;100]
US	< 2 yrs	85/1,062£	All G1P[8] G2P[4]	85 [73;92] 88 [68;95] 88 [68;95]
	8-11 m		All	89 [48;98]
US	< 5 yrs	74/255†	All	68 [34;85]
Middle Income Countries				
Bolivia	< 3 yrs	300/974	All G9P[8] G3P[8] G2P[4] G9P[6]	77 [65;84]* 85 [69;93] 93 [70;98] 69 [14;89] 87 [19;98]
	6-11 m		All G9P[8]	77 [51;89] 90 [65;97]
Brazil	< 2 yrs	115/1,481	All G1P[8] G2P[4]	72 [44;85]* 89 [78;95] 76 [64;84]

Brazil	< 3 yrs	249/249£	All G2P[4]	76 [58;86] 75 [57;86]
	3-11 m		All G2P[4]	96 [68;99] 95 [66;99]±
El Salvador	< 2 yrs	251/770£	All	76 [64;84]*
	6-11 m			83 [68;91]
Mexico	< 2 yrs	9/17£	G9P[4]	94 [16;100]
Low Income Countries				
Malawi	< 2 yrs	81/286£	All	63 [23;83]

yr(s): year(s)
m: months
$ The number of fully vaccinated (2 doses) and unvaccinated cases and controls is given.
† Vaccine effectiveness was calculated using rotavirus-negative hospital control participants (estimates from Taiwan were calculated using combined rotavirus-negative hospital control and non-diarrhoea hospital control participants).
£ Vaccine effectiveness was calculated using neighborhood controls.
* In subjects who did not receive the full course of vaccination, the effectiveness after one dose ranged from 51% (95% CI: 26;67, El Salvador) to 60% (95% CI: 37;75, Brazil).
± Data from a post-hoc analysis

Impact on mortality§

Impact studies with ***Rotarix*** conducted in Panama, Brazil and Mexico showed a decrease in all-cause diarrhoea mortality ranging from 22% to 56% in children less than 5 years of age, within 2 to 3 years after vaccine introduction.

Impact on hospitalisation§

In a retrospective database study in Belgium conducted in children 5 years of age and younger, the direct and indirect impact of ***Rotarix*** vaccination on rotavirus-related hospitalisation ranged from 64% (95% CI: 49;76) to 80% (95% CI: 77;83) two years after vaccine introduction. Similar studies in Brazil, Australia and El Salvador showed a reduction of 45 to 88%.

In addition, two impact studies on all-cause diarrhoea hospitalisation conducted in Latin America showed a reduction of 38 to 40% four years after vaccine introduction.

§NOTE : Impact studies are meant to establish a temporal relationship but not a causal relationship between the disease and vaccination.

Pharmacokinetics

Not relevant for vaccines.

Non-Clinical Information

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

PHARMACEUTICAL INFORMATION

List of Excipients

Sucrose, di-sodium adipate, Dulbecco's Modified Eagle Medium (DMEM), sterile water.

Shelf Life

The expiry date is indicated on the label and packaging.

Storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Store in the original package in order to protect from light.

The storage conditions are detailed on the packaging.

Nature and Contents of Container

1.5 ml of **oral** suspension in an **oral** applicator (Type I, Ph. Eur.) with a plunger stopper (butyl rubber). Pack sizes of 1, 5, 10, 25, 50 or 100.

Not all presentations are available in every country.

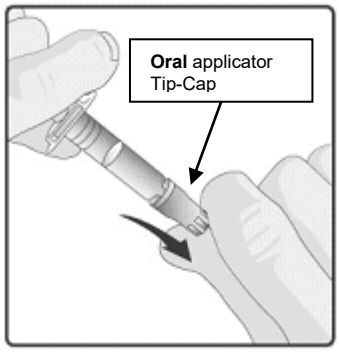
Incompatibilities

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

Use and Handling (see end of the leaflet)

The vaccine is presented as a clear, colourless 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 be inspected visually for any foreign particulate matter and/or abnormal physical appearance. 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.

Instructions for 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.**

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Manufacturer (responsible for batch release):
GlaxoSmithKline Biologicals s.a., Rixensart, Belgium

[GlaxoSmithKline Logo]