

For the use only of registered medical practitioners or a hospital or a laboratory

ROTARIX
Rotavirus Vaccine (Live Attenuated, Oral) IP

1. NAME OF THE MEDICINAL PRODUCT

Rotavirus Vaccine (Live Attenuated, Oral) IP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml (1 dose) of reconstituted vaccine contains:

Human rotavirus RIX4414 strain (live attenuated)..... not less than $10^{6.0}$ CCID₅₀

Cell substrate: Vero cell line

For excipients, see section 6.1 *List of Excipients*.

3. PHARMACEUTICAL FORM

Powder and diluent for oral suspension

The vaccine consists of a freeze-dried preparation (white powder) to be reconstituted with the supplied diluent (turbid liquid) before oral administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

The use of *ROTARIX* should be based on official recommendations.

4.2 Posology and method of 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.

Paediatric population

ROTARIX should not be used in children over 24 weeks of age.

Method of administration

ROTARIX is for **oral** use only.

ROTARIX SHOULD UNDER NO CIRCUMSTANCES BE INJECTED.

For instructions for the preparation or reconstitution of the medicinal product before administration, see section 6.6 *Special precautions for disposal and other handling*.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 *List of excipients*.

Hypersensitivity after previous administration of rotavirus vaccines.

History of intussusceptions.

Subjects with uncorrected congenital malformation of the gastrointestinal tract that would predispose for intussusception.

Subjects with Severe Combined Immunodeficiency (SCID) disorder (see section 4.8 *Undesirable effects*).

Administration of *ROTARIX* should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection is not a contra-indication for immunisation.

The administration of *ROTARIX* should be postponed in subjects suffering from diarrhoea or vomiting.

4.4 Special warnings and precautions for use

It is good clinical practice that vaccination should be preceded by a review of the medical history especially with regard to contraindications and by a clinical examination.

There are no data on the safety and efficacy of *ROTARIX* in infants with gastrointestinal illnesses or growth retardation. 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.

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) since data from observational safety studies indicate an increased risk of intussusception, mostly within 7 days after rotavirus vaccination (see section 4.8 *Undesirable*

effects). Parents/guardians should be advised to promptly report such symptoms to their healthcare provider.

For subjects with a predisposition for intussusception, see section 4.3 *Contraindications*.

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 section 4.8 *Undesirable effects*).

Administration of *ROTARIX* to infants who have known or suspected immunodeficiency should be based on careful consideration of potential benefits and risks.

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% of stools after the first dose and 4% of stools after the second dose. When these stools were tested for the presence of live vaccine strain, only 17% were positive.

Cases of transmission of this excreted vaccine virus to seronegative contacts of vaccines have been observed without causing any clinical symptom.

ROTARIX should be administered with caution to individuals with immunodeficient close contacts, such as individuals with malignancies, or who are otherwise immunocompromised or individuals receiving immunosuppressive therapy.

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

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunisation series, particularly for those with a previous history of respiratory immaturity.

As the benefit of the vaccination is high in this group of infants, vaccination should not be withheld or delayed.

A protective immune response may not be elicited in all vaccines (see section 5.1 *Pharmacodynamic properties*).

The extent of protection that *ROTARIX* might provide against other rotavirus strains that have not been circulating in clinical trials is currently unknown. Clinical studies from which efficacy data were derived were conducted in Europe, Central and South America, Africa and Asia (see section 5.1 *Pharmacodynamic properties*).

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

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

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

The vaccine contains sucrose and sorbitol as excipients. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this vaccine.

4.5 Interaction with other medicinal products and other forms of 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 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.

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

4.6 Pregnancy and lactation

ROTARIX is not intended for use in adults. There are no data on the use of *ROTARIX* during pregnancy and lactation.

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.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

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 (Finland, India and Bangladesh), 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 (Europe, North America, Latin America, Asia, Africa) including trials in which *ROTARIX* was co-administered with routine paediatric vaccines (see section 4.5 *Interaction with other medicinal products and other forms of interactions*), the following adverse reactions (collected 31 days post-vaccination) were considered as possibly related to vaccination.

Tabulated list of adverse reactions

Adverse reactions reported are listed according to the following frequency:

Frequencies are reported as:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$)

System Organ Class	Frequency	Adverse reactions
Gastrointestinal disorders	Common	Diarrhoea
	Uncommon	Abdominal pain, flatulence
	Very rare	Intussusception (see section 4.4 <i>Special warnings and precautions for use</i>)
	Not Known*	Haematochezia
	Not Known*	Gastroenteritis with vaccine viral shedding in infants with Severe Combined Immunodeficiency (SCID) disorder
Skin and subcutaneous tissue disorders	Uncommon	Dermatitis
General disorders and administration site conditions	Common	Irritability
Respiratory, thoracic and mediastinal disorders	Not Known*	Apnoea in very premature infants (≤ 28 weeks of gestation) (see section 4.4 <i>Special warnings and precautions for use</i>)

* Because these events were reported spontaneously, it is not possible to reliably estimate their frequency.

Description of selected adverse reactions

Intussusception

Data from observational safety studies performed in several countries indicate that rotavirus vaccines carry an increased risk of intussusception, mostly within 7 days of vaccination. Up to 6 additional cases per 100,000 infants have been observed in the US and Australia against a background incidence of 33 to 101 per 100,000 infants (less than one year of age) per year, respectively.

There is limited evidence of a smaller increased risk following the second dose.

It remains unclear whether rotavirus vaccines affect the overall incidence of intussusception based on longer periods of follow-up (see section 4.4 *Special warnings and precautions for use*).

Other special populations

Safety in infants with human immunodeficiency (HIV) infection

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

4.9 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*.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: rotavirus diarrhoea vaccines, ATC code: J07BH01.

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.

Clinical protection was assessed in the ATP cohort for efficacy, which includes all subjects from the ATP cohort for safety who entered into the concerned efficacy follow-up period.

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.

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

	1 st year of life <i>ROTARIX</i> N=2,572 Placebo N=1,302		2 nd year of life <i>ROTARIX</i> N=2,554 Placebo N=1,294	
Vaccine efficacy (%) against any and severe rotavirus gastro-enteritis [95% CI]				
Genotype	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 was defined as a score ≥ 11 on the Vesikari scale

* 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 (GE) was defined according to WHO criteria. The protective vaccine efficacy against severe rotavirus (RV) gastro-enteritis requiring hospitalisation and/or rehydration therapy in a medical facility and the genotype specific vaccine efficacy after two doses of *ROTARIX* are presented in the table below:

Genotype	Severe rotavirus gastro-enteritis† (1st year of life) <i>ROTARIX</i> N=9,009 Placebo N=8,858	Severe rotavirus gastro-enteritis† (2nd year of life) <i>ROTARIX</i> 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)

* 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] genotype during the first year of life.

* In these studies, the point estimates and confidence intervals were respectively: 100% (95% CI: -1,858.0;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 (*ROTARIX*: N = 2,974; placebo: N = 1,443) 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 protective vaccine efficacy (pooled doses) observed against any and severe rotavirus gastro-enteritis is presented in the following table:

Genotype	Any rotavirus gastro-enteritis	Severe rotavirus gastro-enteritis†
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	ROTARIX N=2,974 Placebo N=1,443	ROTARIX N=2,974 Placebo N=1,443
	Efficacy (%) [95% CI]	Efficacy (%) [95% CI]
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* [<0.0;83.7]	51.5* [<0.0;96.5]
G8P[4]	38.7* [<0.0;67.8]	63.6 [5.9;86.5]
G9P[8]	41.8* [<0.0;72.3]	56.9* [<0.0;85.5]
G12P[6]	48.0 [9.7;70.0]	55.5* [<0.0; 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* [<0.0;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

* Not statistically significant ($p \geq 0.05$). These data should be interpreted with caution.

Sustained efficacy up to 3 years of age in Asia

A clinical study conducted in Asia (Hong Kong, Singapore and Taiwan) (Total vaccinated cohort: ROTARIX: N = 5,359; placebo: N = 5,349) evaluated ROTARIX given according to different schedules (2, 4 months of age; 3, 4 months of age).

During the first year, significantly fewer subjects in the ROTARIX group reported severe rotavirus gastro-enteritis caused by the circulating wild-type RV compared to the placebo group from 2 weeks after Dose 2 up to one year of age (0.0% versus 0.3%), with a vaccine efficacy of 100% (95% CI: 72.2; 100).

The protective vaccine efficacy after two doses of ROTARIX observed against severe rotavirus gastro-enteritis up to 2 years of age is presented in the following table:

	Efficacy up to 2 years of age ROTARIX N= 5263 Placebo N= 5256
Vaccine efficacy (%) against severe rotavirus gastro-enteritis (95% CI)	
Genotype	Severe†
G1P[8]	100 (80.8;100)
G2P[4]	100* (<0;100)
G3P[8]	94.5 (64.9;99.9)
G9P[8]	91.7 (43.8;99.8)

Strains with P[8] genotype	95.8 (83.8;99.5)
Circulating rotavirus strains	96.1 (85.1;99.5)
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)

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

* Not statistically significant ($p \geq 0.05$). These data should be interpreted with caution

During the third year of life, there were no cases of severe RV gastro-enteritis in the *ROTARIX* group (N=4,222) versus 13 (0.3%) in the placebo group (N=4,185). Vaccine efficacy was 100% (95% CI: 67.5; 100). The severe RV gastro-enteritis cases were due to RV strains G1P[8], G2P[4], G3P[8] and G9P[8]. The incidence of severe RV gastro-enteritis associated with the individual genotypes was too small to allow calculation of efficacy. The efficacy against severe RV gastro-enteritis requiring hospitalisation was 100% (95% CI: 72.4; 100).

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) with serum anti-rotavirus IgA antibody titers ≥ 20 U/ml one to two months after the second dose of vaccine or placebo as observed in different studies.

Schedule	Studies conducted in	Vaccine		Placebo	
		N	% ≥ 20 U/ml [95% CI]	N	% ≥ 20 U/ml [95% CI]
2, 3 months	France, Germany	239	82.8 [77.5;87.4]	127	8.7 [4.4;15.0]
2, 4 months	Spain	186	85.5 [79.6;90.2]	89	12.4 [6.3;21.0]
3, 5 months	Finland, Italy	180	94.4 [90.0;97.3]	114	3.5 [1.0;8.7]
3, 4 months	Czech Republic	182	84.6 [78.5;89.5]	90	2.2 [0.3;7.8]
2, 3 to 4 months	Latin America; 11 countries	393	77.9% [73.8;81.6]	341	15.1% [11.7;19.0]
10, 14 weeks and 6, 10, 14 weeks (Pooled)	South Africa, Malawi	221	58.4 [51.6;64.9]	111	22.5 [15.1;31.4]

Effectiveness

In observational studies, vaccine effectiveness was demonstrated against severe gastro-enteritis leading to hospitalization due to rotavirus of common genotypes G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8] as well as the less common rotavirus genotypes G9P[4] and G9P[6]. All of these strains are circulating worldwide.

Effectiveness after 2 doses in preventing RVGE leading to hospitalization

Countries Period	Age range	N ⁽¹⁾ (cases/controls)	Strains	Effectiveness % [95% CI]
High Income countries				
Belgium 2008- 2010 ⁽²⁾	< 4 yrs 3-11 m	160/198	All	90 [81;95] 91 [75;97]
	< 4 yrs	41/53	G1P[8]	95 [78;99]
	< 4 yrs 3-11 m	80/103	G2P[4]	85 [64;94] 83 [11;96] ⁽³⁾
	< 4 yrs	12/13	G3P[8]	87* [<0 ;98] ⁽³⁾
	< 4 yrs	16/17	G4P[8]	90 [19;99] ⁽³⁾
Singapore 2008- 2010 ⁽²⁾	< 5 yrs	136/272	All	84 [32;96]
		89/89	G1P[8]	91 [30;99]
Taiwan 2009-2011	< 3 yrs	275/1,623 ⁽⁴⁾	All G1P[8]	92 [75;98] 95 [69;100]
US 2010-2011	< 2 yrs	85/1,062 ⁽⁵⁾	All G1P[8] G2P[4]	85 [73;92] 88 [68;95] 88 [68;95]
	8-11 m		All	89 [48;98]
US 2009-2011	< 5 yrs	74/255 ⁽⁴⁾	G3P[8]	68 [34;85]
Middle Income Countries				
Bolivia 2010-2011	< 3 yrs 6-11 m	300/974	All	77 [65;84] ⁽⁶⁾ 77 [51;89]
			G9P[8]	85 [69;93] 90 [65;97]
	< 3 yrs 6-11 m			G3P[8]
			G2P[4]	69 [14;89]
			G9P[6]	87 [19;98]
	< 3 yrs		All	72 [44;85] ⁽⁶⁾
			G1P[8]	89 [78;95]
G2P[4]		76 [64;84]		
Brazil 2008- 2009 ⁽²⁾	< 3 yrs 3-11 m	249/249 ⁽⁵⁾	All	76 [58;86] 96 [68;99]
	< 3 yrs 3-11 m	222/222 ⁽⁵⁾	G2P[4]	75 [57;86] 95 [66;99] ⁽³⁾
El Salvador 2007-2009	< 2 yrs 6-11 m	251/770 ⁽⁵⁾	All	76 [64;84] ⁽⁶⁾ 83 [68;91]
Guatemala 2012-2013	< 4 yrs	NA ⁽⁷⁾	All	63 [23;82]

Mexico 2010	< 2 yrs	9/17 ⁽⁵⁾	G9P[4]	94 [16;100]
Low Income Countries				
Malawi 2012-2014	< 2 yrs	81/234 ⁽⁵⁾	All	63 [23;83]

m: months

yrs: years

* Not statistically significant ($P \geq 0.05$). These data should be interpreted with caution.

(1) The number of fully vaccinated (2 doses) and unvaccinated cases and controls is given.

(2) GSK sponsored studies

(3) Data from a post-hoc analysis

(4) 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).

(5) Vaccine effectiveness was calculated using neighborhood controls.

(6) 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).

(7) NA: not available. Vaccine effectiveness estimate is based on 41 fully vaccinated cases and 175 fully vaccinated controls.

Impact on mortality[§]

Impact studies with *ROTARIX* conducted in Panama, Brazil and Mexico showed a decrease in all cause diarrhoea mortality ranging from 17% to 73% in children less than 5 years of age, within 2 to 4 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 Armenia, Australia, Brazil, Canada, El Salvador and Zambia showed a reduction of 45 to 93% between 2 and 4 years from vaccine introduction.

In addition, nine impact studies on all cause diarrhoea hospitalisation conducted in Africa and Latin America showed a reduction of 14% to 57% between 2 and 5 years after vaccine introduction.

[§]NOTE: Impact studies are meant to establish a temporal relationship but not a causal relationship between the disease and vaccination. Natural fluctuations of the incidence of the disease may also influence the observed temporal effect.

5.2 Pharmacokinetic properties

Not applicable

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Sucrose, Dextran, Sorbitol, Amino acids, Dubelcco's Modified Eagle Medium (DMEM)

Diluent

Calcium carbonate, Xanthan, Water for Injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf-life

36 months

After reconstitution:

After the reconstitution, the vaccine should be administered immediately. If not used immediately, in-use storage should not be longer than 24 hours and at a temperature between 2-25°C.

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

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Store in the original package in order to protect from light

For storage conditions after reconstitution of the medicinal product, see section 6.3 *Shelf life*.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

1 dose of powder in glass container (Type I glass) with a stopper (rubber butyl)

1 ml of diluent in an **oral** applicator (Type I glass) with a plunger stopper and a protective tip cap (rubber butyl).

Transfer adapter for reconstitution (1/dose) in the following pack sizes:

- pack size of 1 glass container of powder plus 1 **oral** applicator of diluent
- pack size of 5 glass containers of powder plus 5 **oral** applicators of diluent
- pack size of 10 glass containers of powder plus 10 **oral** applicators of diluent
- pack size of 25 glass containers of powder plus 25 **oral** applicators of diluent
- pack size of 50 glass containers of powder plus 50 **oral** applicators of diluent
- pack size of 100 glass containers of powder plus 100 **oral** applicators of diluent

All presentations may not be marketed in the Country.

6.6 Special precautions for disposal and other handling

Before reconstitution:

A white deposit and clear supernatant is observed upon storage of the **oral** applicator containing the diluent. The diluent should be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to reconstitution.

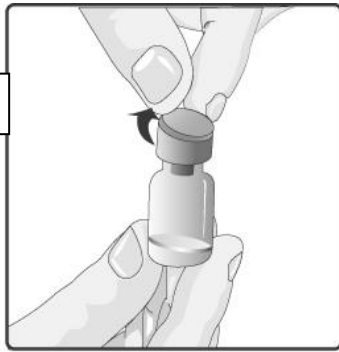
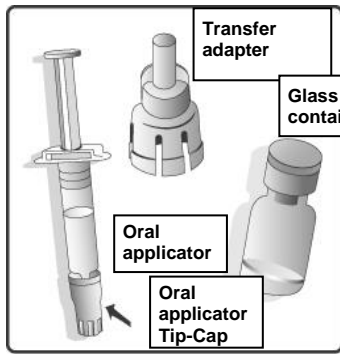
After reconstitution

The reconstituted vaccine is slightly more turbid than the diluent and is milky white in appearance

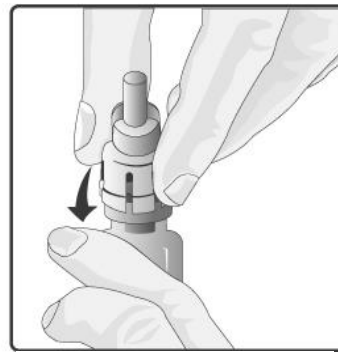
The reconstituted vaccine should also be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, discard the vaccine.

Any unused vaccine or waste material should be disposed of in accordance with local requirements.

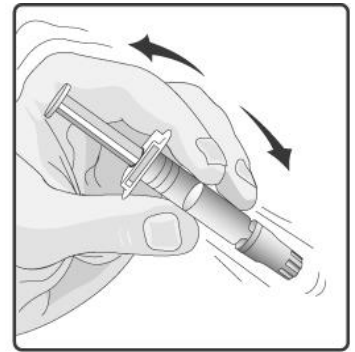
Instructions for reconstitution and administration of the vaccine:



1. Remove the plastic cover from the glass container containing the powder



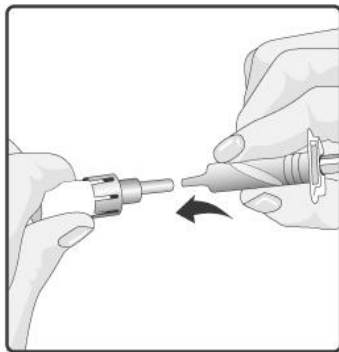
2. Connect the transfer adapter onto the glass container by pushing it downwards until the transfer adapter is properly and securely placed



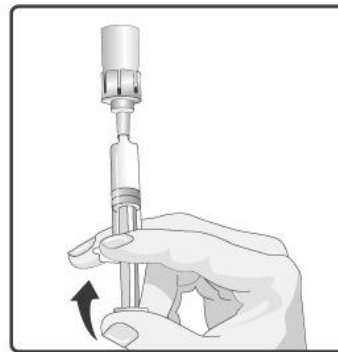
3. Shake the oral applicator containing the diluent vigorously. The shaken suspension will appear as a turbid liquid with a slow settling white deposit



4. Remove the protective tip cap from the oral applicator



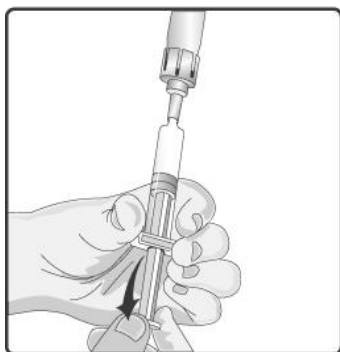
5. Connect the oral applicator into the transfer adapter by pushing it firmly on this device



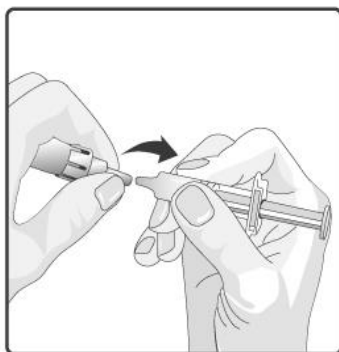
6. Transfer the entire content of the oral applicator into the glass container containing the powder



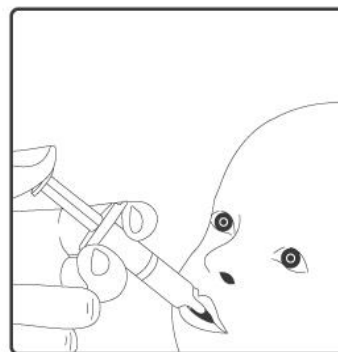
7. With the oral applicator still attached, shake the glass container and examine it for complete suspension of the powder. The reconstituted vaccine will appear more turbid than the diluent alone. This appearance is normal



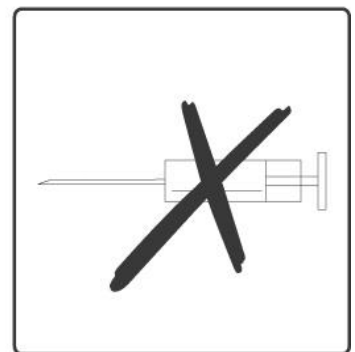
8. Withdraw the entire mixture back into the oral applicator



9. Remove the oral applicator from the transfer adapter



10. This vaccine is for oral administration only. The child should be seated in a reclining position. Administer the entire content of the oral applicator ORALLY (by administering the entire content of the oral applicator on the inside of the cheek)



11. Do not inject.

If the reconstituted vaccine is to be stored temporarily before administration, replace the protective tip cap on the **oral** applicator. The **oral** applicator containing the reconstituted vaccine should be shaken gently again before **oral** administration. **Do not inject.**

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Pharmaceuticals Limited
Registered Office
 Dr. Annie Besant Road, Worli
 Mumbai 400 030, India.

8. MARKETING AUTHORISATION NUMBER(S)

Import Permission No.: Import-8105/07.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization (Form 45): 19th November, 2007.

Trademarks are owned by or licensed to the GSK group of companies.

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