

PRODUCT INFORMATION

Rotavirus vaccine – live attenuated oral

NAME OF THE MEDICINE

ROTARIX

Human rotavirus (live attenuated oral vaccine) oral liquid

DESCRIPTION

ROTARIX is a liquid suspension of the live attenuated RIX4414 strain of human rotavirus of the G1P[8] type for use in the prevention of rotavirus gastro-enteritis. The virus strain derived from the 89-12 strain is obtained by propagation on a well-characterised Vero cell line.

ROTARIX is presented as a clear, colourless liquid, free of visible particles, for ORAL administration only.

Each 1.5 mL dose of the vaccine contains not less than $10^{6.0}$ CCID₅₀ (cell culture infectious dose 50%) of the RIX 4414 strain of human rotavirus. The vaccine also contains sucrose, di-sodium adipate, Dulbecco's Modified Eagle Medium and sterile water.

The manufacture of this product includes exposure to bovine derived materials at the very early steps of the production process. No bovine materials are used in routine production. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

CLINICAL PHARMACOLOGY

Rotavirus is likely to affect all children up to the age of five years of age. The peak incidence of rotavirus gastro-enteritis is between 6-24 months of age. Dehydration from rotavirus gastro-enteritis can lead to hospitalisation, which is most common in children under 2 years of age.

Mechanism of Action

The immunologic mechanism by which *ROTARIX* protects against rotavirus gastro-enteritis is not entirely understood. A relationship between antibody responses to rotavirus vaccination and protection against rotavirus gastro-enteritis has not been established. *ROTARIX*, which is derived from the most common human rotavirus type G1P[8], has been demonstrated to induce protective immunity against both the G1P[8] type, and also against other non-G1 prevalent strains (See Clinical Trials).

CLINICAL TRIALS

Protective efficacy of the ROTARIX lyophilised formulation

Clinical studies have been conducted in Europe and Latin America to evaluate the protective efficacy of *ROTARIX* against any and severe rotavirus gastro-enteritis in countries with different levels of burden of disease. Protective efficacy has been shown to be higher against severe rotavirus gastroenteritis than rotavirus gastroenteritis of any severity. Protective efficacy has been demonstrated against rotavirus of types G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8] .

A clinical study performed in Europe evaluated *ROTARIX* given according to different European schedules (2, 3months; 2, 4 months; 3, 4 months; 3, 5 months) in 3,994 subjects (2646 subjects receiving *ROTARIX* and 1348 subjects receiving placebo). 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. The first dose was given between 6 and 14 weeks of age and the second dose was administered 4 to 8 weeks later.

After two doses of *ROTARIX*, the protective vaccine efficacy observed during the first and second year of life and the two years combined is presented in Table 1.

Table 1: Efficacy following two doses of *ROTARIX* persisting during the first and second year of life and the two years combined - European study

	1 st Year of life ³		2 nd Year of life ⁴		1 st and 2 nd Year of life combined ³	
	Efficacy (%)	95% CI ²	Efficacy (%)	95% CI ²	Efficacy (%)	95% CI ²
Any rotavirus gastro-enteritis	87.1*	79.6;92.1	71.9*	61.2;79.8	78.9*	72.7;83.8
Severe rotavirus gastro-enteritis¹	95.8*	89.6;98.7	85.6*	75.8;91.9	90.4*	85.1;94.1
Rotavirus gastro-enteritis requiring medical attention	91.8*	84;96.3	76.2*	63.0;85.0	83.8*	76.8;88.9
Hospitalisation due to rotavirus gastro-enteritis	100*	81.8;100	92.2*	65.6;99.1	96.0*	83.8;99.5
1. Severe gastro-enteritis defined as a score ≥ 11 on the Vesikari scale 2. CI: Confidence Interval 3. <i>ROTARIX</i> N=2572, Placebo N= 1302 (§) 4. <i>ROTARIX</i> N=2554, Placebo N= 1294 (§) (§) ATP cohort for efficacy * Statistically significant ($p < 0.05$)						

The type specific vaccine efficacy is presented in Table 2 below:

Table 2: Efficacy of ROTARIX lyophilised formulation against any and severe rotavirus gastro-enteritis – European study

Type	1 st Year of life				2 nd Year of life				1 st and 2 nd Year of life combined			
	All rotavirus gastro-enteritis		Severe rotavirus gastro-enteritis ¹		All rotavirus gastro-enteritis		Severe rotavirus gastro-enteritis ¹		All rotavirus gastro-enteritis		Severe rotavirus gastro-enteritis ¹	
	Efficacy ²	95% CI ³	Efficacy ²	95% CI ³	Efficacy ²	95% CI ³	Efficacy ²	95% CI ³	Efficacy ²	95% CI ³	Efficacy ²	95% CI ³
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	89.5*	82.5; 94.1	96.4*	90.4; 99.1
G2P[4]	62.0	-124.4; 94.4	74.7	-386.2; 99.6	57.1*	-3.7; 82.6	89.9*	9.4; 99.8	58.3*	10.1; 81.0	85.5*	24.0; 98.5
G3P[8]	89.9*	9.5; 99.8	100.0*	44.8; 100.0	79.7*	-23.8; 98.1	83.1	-110.3; 99.7	84.8*	41.0; 97.3	93.7*	52.8; 99.9
G4P[8]	88.3*	57.5; 97.9	100.0*	64.9; 100.0	69.6	-56.2; 95.3	87.3*	-28.0; 99.7	83.1*	55.6; 94.5	95.4*	68.3; 99.9
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	72.5*	58.6; 82.0	84.7*	71.0; 92.4
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	81.8*	75.8; 86.5	91.9*	86.8; 95.3
1. Severe gastro-enteritis defined as a score ≥ 11 on the Vesikari scale 2. Efficacy (%): Vaccine efficacy defined as 1-stratified Poisson rate ratio 3. CI: Confidence Interval * Statistically significant ($p < 0.05$)												

When the severity of rotavirus gastro-enteritis was scored using the 20-point Vesikari scale, 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 .

Although *ROTARIX* is a 2-dose vaccine, efficacy has been observed as from the first dose. In Europe, vaccine efficacy against rotavirus gastro-enteritis of any severity from dose 1 up to dose 2 was 89.8% (95% CI: 8.9; 99.8).

A clinical study performed in Latin America evaluated *ROTARIX* in more than 20,000 subjects. The first dose was given between 6 and 12 weeks of age and the second dose was administered 4 to 8 weeks later. After two doses of *ROTARIX*, the protective vaccine efficacy against severe rotavirus gastro-enteritis requiring hospitalisation and/or rehydration therapy in a medical facility was 84.7% (95% CI: 71.7; 92.4). Protective efficacy of *ROTARIX* was maintained during the second year of life with a vaccine efficacy against severe rotavirus gastro-enteritis of 79.0% (95% CI: 66.4; 87.4).

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

Immunogenicity of the ROTARIX liquid formulation

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 in terms of anti-rotavirus IgA antibody seroconversions and geometric mean concentrations.

INDICATIONS

ROTARIX is indicated for the prevention of rotavirus gastroenteritis (see Clinical Trials).

CONTRAINDICATIONS

ROTARIX should not be administered to subjects with known hypersensitivity to any components of the vaccine (see DESCRIPTION), or to subjects having shown signs of hypersensitivity after previous administration of rotavirus vaccines.

ROTARIX should not be administered to subjects with any history of chronic gastrointestinal disease including any uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract.

As with other vaccines, administration of *ROTARIX* should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, such as a cold, is not a contraindication for immunisation.

PRECAUTIONS

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

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

Administration of *ROTARIX* may be considered with caution in infants with gastrointestinal illnesses, when, in the opinion of the physician, the risk of rotavirus infection by withholding the vaccine entails a greater risk to the infant. No safety or efficacy data are available for the administration of *ROTARIX* to infants with gastrointestinal illnesses.

No safety data are available in subjects with primary and secondary immunodeficiency states including HIV positive infants.

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 ADVERSE REACTIONS). In post-marketing experience, cases of intussusception have been reported in temporal association with *ROTARIX*. Most cases were reported within seven days following the first dose. No causal relationship has been established.

Excretion of the vaccine virus in the stools occurs 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, 17% were positive. In two comparative controlled trials, vaccine shedding after vaccination with *ROTARIX* liquid formulation was comparable to that observed after vaccination with *ROTARIX* lyophilised formulation. There is a potential risk for transmission to non-vaccinated contacts. Therefore *ROTARIX* should be administered with caution to infants with close contacts who are immunodeficient, such as household members who are immunocompromised or receiving immunosuppressive therapy. Contacts of recent vaccinees should be advised to observe personal hygiene (e.g. wash their hands after changing child's nappies).

In data gathered from 140 premature infants between 29 and 36 weeks gestation, the vaccine was well tolerated. The level of clinical protection remains unknown.

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

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

Carcinogenicity and Mutagenicity

ROTARIX has not been evaluated for carcinogenicity or mutagenicity.

Impairment of Fertility

ROTARIX has not been evaluated for its potential to impair fertility.

Genotoxicity

ROTARIX has not been evaluated for genotoxicity.

Use in Pregnancy (Category B2):

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

Use in Lactation:

ROTARIX is not intended for use in adolescents or adults. Thus human data on use during lactation are not available.

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.

Paediatric Use

ROTARIX is intended for use in infants in the first six months of life. *ROTARIX* should not be administered to children older than 24 weeks of age as safety has not been demonstrated, particularly in relation to risk of intussusception.

Use in the Elderly

ROTARIX is not intended for use in the elderly. Thus human data on use in the elderly are not available.

Interactions

Co-administration studies have demonstrated that *ROTARIX* can be given concomitantly with any of the following administered either as monovalent or as combination vaccines: diphtheria-tetanus-acellular pertussis vaccine (DTPa), *Haemophilus influenzae* type b vaccine (Hib), inactivated polio vaccine (IPV), hepatitis B vaccine (HBV), hexavalent vaccines DTPa-HBV-IPV/Hib, pneumococcal conjugate vaccine and meningococcal serogroup C conjugate vaccine. The studies demonstrated that the immune responses and the safety profiles of the administered vaccines were unaffected.

Clinical studies, involving more than 2,000 subjects, were performed where *ROTARIX* and oral polio vaccine (OPV) were administered two weeks apart. The immune response to *ROTARIX* and OPV was unaffected. In three immunogenicity studies, involving approximately 1,200 subjects, *ROTARIX* was concomitantly administered with OPV. The immune response to OPV, as well as the response to *ROTARIX* after the second dose, were unaffected. *ROTARIX* can be concomitantly administered with OPV if this is in accordance with local recommendations. In the absence of local recommendations, an interval of two weeks between the administration of OPV and *ROTARIX* should be respected.

Although antibodies to rotavirus may be detected in breast milk, the available data show no reduction in efficacy when *ROTARIX* is administered to breast-fed infants.

Effects on laboratory tests

ROTARIX has not been evaluated for effects on laboratory tests.

ADVERSE REACTIONS

Clinical Trial Experience with *ROTARIX* lyophilised formulation

A total of eleven placebo-controlled clinical trials involved the administration of more than 77,800 doses of *ROTARIX* to approximately 40,200 infants in the first six months of life. In two clinical trials, *ROTARIX* was administered alone. In other clinical trials, *ROTARIX* was co-administered with other paediatric vaccines (see Interactions).

ROTARIX is generally well tolerated.

In two clinical trials (Finland), ROTARIX was administered alone (administration of routine paediatric vaccines was staggered). The incidence of diarrhoea, fever and irritability was comparable to the control group receiving placebo. No increase in the incidence or severity of these events was seen with the second dose.

In the other nine clinical trials, (Europe, Canada, USA, Latin America, Singapore, South-Africa), ROTARIX was co-administered with other paediatric vaccines (see Interactions). The adverse reaction profile observed in these subjects was comparable to the subjects receiving the same paediatric vaccines and placebo.

Table 3: ROTARIX lyophilised vaccine - Adverse reactions per system organ class and frequency within a maximum of 43 days after vaccination

System Organ Class	Preferred term	Incidence in the ROTARIX group (%)	Incidence in the placebo group (%)
Infections and infestations	upper respiratory tract infection	0.10	0.07
Psychiatric disorders	irritability	45.8	41.8
	crying	0.39	0.52
	sleep disorder	0.39	0.52
Nervous system disorders	somnolence	0.39	0.00
Respiratory, thoracic and mediastinal disorders	hoarseness	0.02	0.00
	rhinorrhoea	0.02	0.00
Gastrointestinal disorders	loss of appetite	15.9	11.5
	diarrhoea	5.1	3.4
	vomiting	8.5	9.7
	flatulence	2.07	0.78
	abdominal pain	1.3	0.52
	regurgitation of food	2.20	1.55
	constipation	0.52	0.00
Skin and subcutaneous tissue disorders	dermatitis	0.04	0.03
	rash	0.03	0.03
Musculoskeletal and connective tissue disorders	muscle cramp	0.02	0.00
General disorders and administration site conditions	fever*	9.2	6.8
	fatigue	1.30	2.58

*rectal temperature >38°C

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.

Table 4: Confirmed cases of intussusception in recipients of *ROTARIX* lyophilised vaccine as compared with placebo recipients (Rota-023)

	<i>ROTARIX</i>	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

Clinical Trial Experience with *ROTARIX* liquid formulation

In a total of four clinical trials, approximately 3,800 doses of *ROTARIX* liquid formulation were administered to approximately 1,930 infants. These trials have shown that the safety and reactogenicity profile of the liquid formulation is comparable to the lyophilised formulation.

Post-marketing data

Rare: haematochezia

DOSAGE AND ADMINISTRATION

Dosage

The vaccination course consists of two doses. The first dose should be given between 6 and 14 weeks of age. The interval between the two doses should not be less than 4 weeks. The vaccine course should be completed by the age of 24 weeks as safety has not been assessed in older children.

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 strongly recommended that infants who receive a first dose of *ROTARIX* complete the 2-dose regimen with *ROTARIX*.

Administration

ROTARIX is for ORAL use only.

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.

Instructions for use and handling

The vaccine is presented as a clear, colourless liquid, free of visible particles, for ORAL administration only. The vaccine is ready to use (no reconstitution or dilution is required).

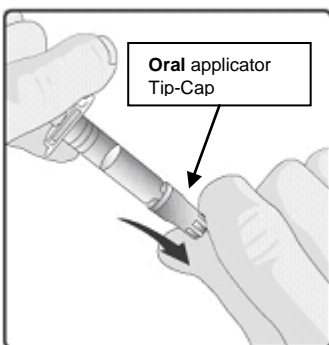
The vaccine is to be administered ORALLY without mixing with any other vaccines or solutions.

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 in oral applicator (syringe-type applicator with a plunger stopper):

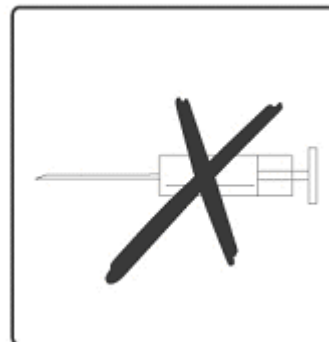
1. Remove the protective tip cap from the oral applicator.
2. This vaccine is for oral administration only. The child should be seated in a reclining position. Administer orally (i.e. into the child's mouth towards the inner cheek) the entire content of the oral applicator.
3. Do not inject.



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.



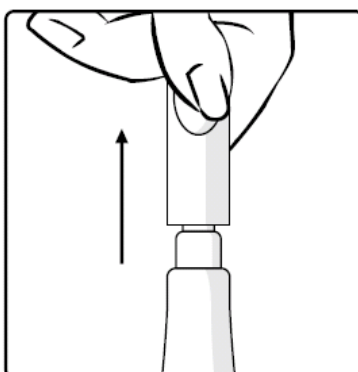
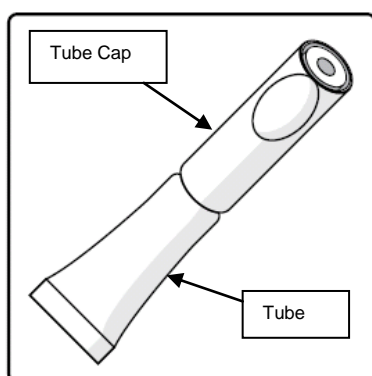
3. **Do not inject.**

Discard the empty oral applicator and tip cap according to local regulations.

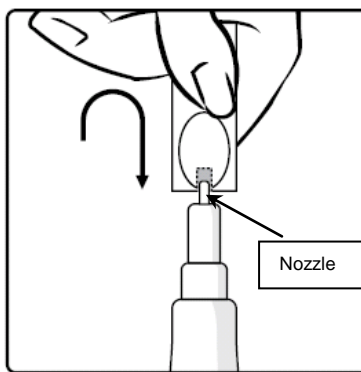
Instructions for administration of the vaccine in tube (Presentation currently not available):

1. Pull off the cap from the top of the tube.
2. Turn the cap upside-down, replace the cap vertically over the nozzle as shown.

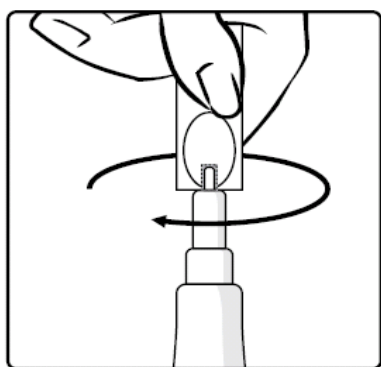
3. Twist the cap to remove the nozzle (do not snap it off) to leave a clean hole through which the vaccine can be expelled.
4. Ensures that the nozzle has been properly removed. A hole should clearly appear at the top of the tube and the nozzle should be inside the top of the tube's cap.
In the event that the nozzle falls into the tube, discard the vaccine. This is a precaution, however, as it is unlikely that the nozzle could be expelled from the tube.
5. 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 tube by gently squeezing the tube several times. (A residual drop may remain in the tip of the tube).



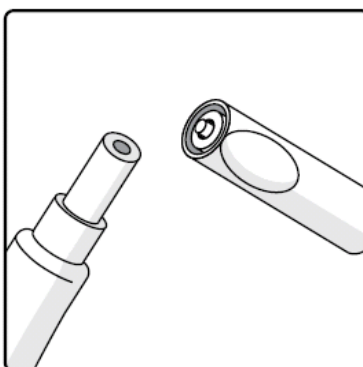
1. Pull off the cap from the top of the tube.



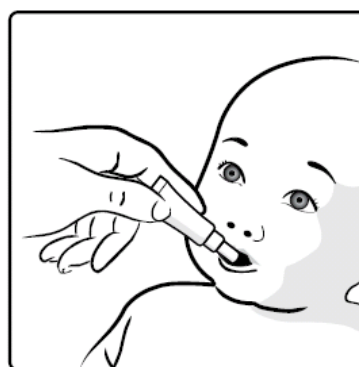
2. Turn the cap upside-down, replace the cap vertically over the nozzle as shown.



3. Twist the cap to remove the nozzle (do not snap it off) to leave a clean hole through which the vaccine can be expelled.



4. Ensures that the nozzle has been properly removed. A hole should clearly appear at the top of the tube and the nozzle should be inside the top of the tube's cap.
In the event that the nozzle falls into the tube, discard the vaccine. This is a precaution, however, as it is unlikely that the nozzle could be expelled from the tube.



5. 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 tube by gently squeezing the tube several times. (A residual drop may remain in the tip of the tube).

Discard the empty tube and cap according to local regulations.

OVERDOSAGE

No cases of overdose have been reported.

Contact Poisons Information Centre (131126) for advice regarding management of overdose.

PRESENTATION AND STORAGE CONDITIONS

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*

1.5 mL of oral suspension in a squeezable tube (LDPE) fitted with a nozzle and a cap (polypropylene). Pack sizes of 1 or 10.

* Presentations not currently marketed

Not currently available

Store at 2°C to 8°C (Refrigerate. Do not freeze). Store in the original package, in order to protect from light.

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline Australia Pty Ltd,
1061 Mountain Hwy
Boronia VIC 3155

DISTRIBUTED IN NEW ZEALAND BY:

GlaxoSmithKline NZ Limited
Auckland NZ

POISON SCHEDULE OF THE DRUG

Schedule 4.

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