

DATASHEET
ROTARIX® ORAL VACCINE
Rotavirus Oral Vaccine, liquid formulation

NAME OF THE MEDICINE

Rotavirus vaccine

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.

Porcine Circovirus type 1 (PCV-1) material has been detected in *ROTARIX* vaccine. PCV-1 is not known to cause disease in animals and is not known to infect or cause disease in humans. There is no evidence that the presence of PCV-1 poses a safety risk.

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, Latin America and Africa 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.

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. Rotarix N=2572, Placebo N= 1302 (§) 4. Rotarix 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 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	95% CI	Efficacy	95% CI	Efficacy	95% CI ³	Efficacy ²	95% CI ³	Efficacy	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).

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 (scored using the 20-point Vesikari scale) 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 Table 3.

Table 3: Efficacy of ROTARIX lyophilised formulation against any and severe rotavirus gastro-enteritis – African study

Strain	Any rotavirus gastro-enteritis (1 st year of life - Pooled results) Rotarix N=2,974 Placebo N=1,443	Severe rotavirus gastro-enteritis (1 st year of life - Pooled results) 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;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]

* Statistically significant (p < 0.05)

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

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

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.

Subjects with Severe Combined Immunodeficiency (SCID) disorder (see ADVERSE REACTIONS).

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.

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).

However, post-marketing safety data indicate a possible increased risk of intussusception in the 31-day period following the administration of the first dose of *ROTARIX*. It has not been established whether *ROTARIX* affects the overall incidence of intussusception. (See ADVERSE REACTIONS).

Therefore, 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.

Administration of *ROTARIX* in immunosuppressed infants, including infants on immunosuppressive therapy, should be based on careful consideration of potential benefits and risks.

Excretion of the vaccine virus in the stools occurs after vaccination and lasts for 10 days on average 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.

In clinical trials, cases of transmission of excreted vaccine virus to seronegative contacts of vaccinees have been observed without causing any clinical symptoms. Therefore *ROTARIX* should be administered with caution to infants with close contacts who are immunodeficient, 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.

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

The extent of protection that *ROTARIX* might provide against rotavirus strains that have not been circulating in clinical trials is currently unknown (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

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

- Very common $\geq 1/10$
- Common $\geq 1/100$ and $< 1/10$
- Uncommon $\geq 1/1000$ and $< 1/100$
- Rare $\geq 1/10,000$ and $< 1/1000$
- Very rare $< 1/10,000$

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

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.

ROTARIX is generally well tolerated.

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, of 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 trials (Europe, North America, Latin America, Asia, Africa) including trials in which *ROTARIX* was co-administered with routine paediatric vaccines (see INTERACTIONS), the following adverse reactions were considered as possibly related to vaccination.

Gastrointestinal disorders:

Common: diarrhoea

Uncommon: flatulence, abdominal pain

Skin and subcutaneous tissue disorders:

Uncommon: dermatitis

The risk of intussusception has been evaluated in a large safety trial conducted in Latin America and Finland where 63,225 infants 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)

	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

Safety in preterm infants

In a clinical study, 1009 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 with 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.

Safety in infants with human immunodeficiency (HIV) infection

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

Post-marketing data

Gastrointestinal disorders:

Rare: intussusception*

haematochezia

gastroenteritis with vaccine viral shedding in infants with Severe Combined Immunodeficiency (SCID) disorder.

*Preliminary data from a large post-marketing epidemiological safety study in Mexico indicate a possible increased risk of intussusception in the 31 day period following the first dose. The relative incidence of intussusception with *ROTARIX* in the 31 day period following the administration of the first dose was 1.752 (99%CI 0.997-3.08) compared to the remaining period up to 1 year of age. Spontaneous reports of intussusception have been received mostly within 7 days after the first dose. These observations are limited to the first dose and not seen following administration of the second dose. It has not been established whether *ROTARIX* affects the overall incidence of intussusception (see PRECAUTIONS).

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.

ROTARIX may be given to preterm infants with the same posology (see Adverse reactions).

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).

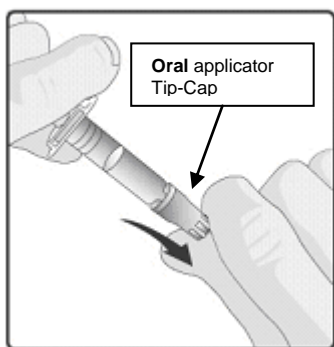
The vaccine is to be administered ORALLY without mixing with any other vaccines or solutions.

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):

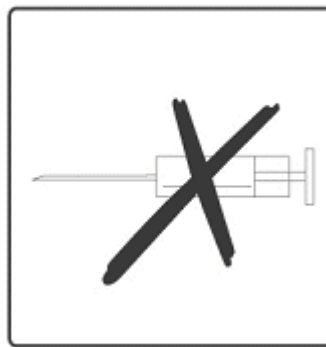
1. Remove the protective tip cap from the oral applicator.
2. This vaccine is for oral administration only. The child should be seated in a reclining position. Administer orally (i.e. into the child's mouth towards the inner cheek) the entire content of the oral applicator.
3. Do not inject.



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.**

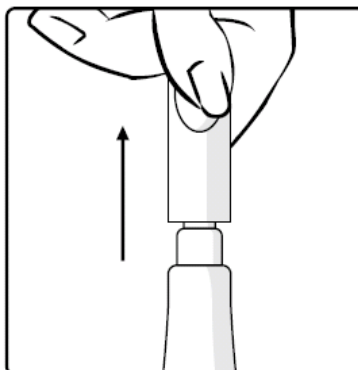
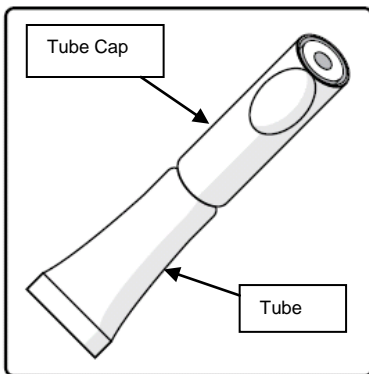
Discard the empty oral applicator and tip cap according to local regulations.

Instructions for administration of the vaccine in tube:

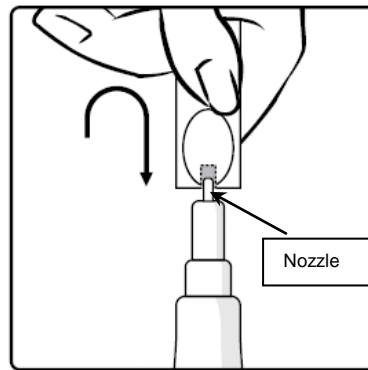
1. Pull off the cap from the top of the tube.
2. Turn the cap upside-down, replace the cap vertically over the nozzle as shown.
3. Twist the cap to remove the nozzle (do not snap it off) to leave a clean hole through which the vaccine can be expelled.
4. Ensures that the nozzle has been properly removed. 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.

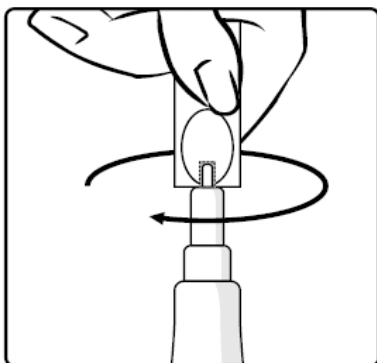
5. This vaccine is for oral administration only. The child should be seated in a reclining position. Administer orally (i.e. into the child's mouth towards the inner cheek) the entire content of the tube by gently squeezing the tube several times. (A residual drop may remain in the tip of the tube).



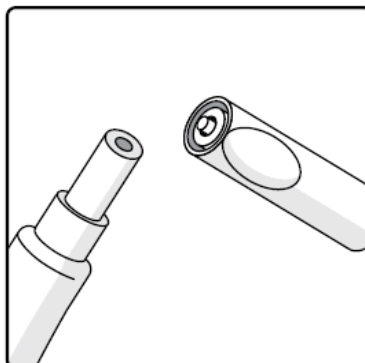
1. Pull off the cap from the top of the tube.



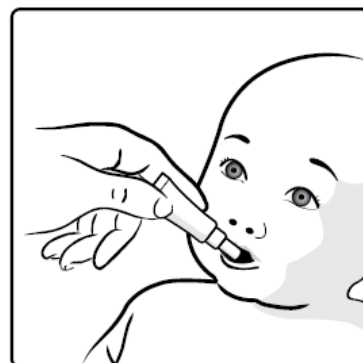
2. Turn the cap upside-down, replace the cap vertically over the nozzle as shown.



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.

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

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

DISTRIBUTED IN NEW ZEALAND BY:

GlaxoSmithKline NZ Limited
AMP Centre
Cnr Albert & Customs Street
Private Bag 106600
Downtown
Auckland

MEDICINE CLASSIFICATION

Prescription Medicine

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