ROTARIX LIQUID ORAL

DO NOT INJECT. FOR ORAL USE ONLY.

SCHEDULING STATUS:
S2

PROPRIETARY NAME AND DOSAGE FORM:
ROTARIX® LIQUID ORAL VACCINE. Rotavirus vaccine. Oral suspension.

COMPOSITION:
1 dose (1,5 ml) contains:
Live attenuated human rotavirus RIX4414 strain not less than $10^{6,0}$ $CCID_{50.}$

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

Residues:
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.

PHARMACOLOGICAL CLASSIFICATION:
A 30.2 Antigens

PHARMACOLOGICAL ACTION:
Pharmacodynamic properties:
Studies on protective efficacy of the ROTARIX LIQUID ORAL VACCINE are not available. The efficacy profile of the new ROTARIX LIQUID ORAL VACCINE is expected to be similar to the currently registered ROTARIX Lyophilized Vaccine formulation, based on comparable immunogenicity data between the two formulations.

Immune response:
In three comparative controlled trials, the immune response elicited by ROTARIX LIQUID ORAL VACCINE was comparable to the one elicited by ROTARIX lyophilised formulation.
The immunologic mechanism by which ROTARIX ORAL VACCINE 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 < 20 U/ml (by ELISA)) and with serum anti-rotavirus IgA antibody titers ≥ 20 U/ml one or two months after the second dose of vaccine or placebo as observed in different studies conducted with ROTARIX lyophyhilised formulation.

Table: Seroconversion for anti-rotavirus IgA antibody after ROTARIX vaccination:

Schedule	Studies conducted in Europe	Vaccine (N=794)	Placebo (N=422)
2, 3 months	France Germany	84,3 % 82,1 %	14 % 6,0 %
2, 4 months	Spain	85,5 %	12,4 %
3, 5 months	Finland Italy	94,6 % 92,3 %	2,9 % 11,1 %
3, 4 months	Czech Republic	84,6 %	2,2 %
Schedule	Studies conducted in Latin America	Vaccine (N=1023)	Placebo (N=428)

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 Hong Kong	100 % 95,2 %	4,5 % 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 %

Immune response in preterm infants:
In a clinical study conducted in preterm infants, ROTARIX was immunogenic; 85,7 % of subjects achieved serum anti-rotavirus IgA antibody titers ≥ 20 U/ml (by ELISA) one month after the second dose of vaccine.

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.

Vaccine shedding:
In two comparative controlled trials, vaccine shedding after vaccination with ROTARIX LIQUID ORAL VACCINE was comparable to that observed after vaccination with ROTARIX lyophilised formulation**.**
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.

Protective efficacy:
Protective efficacy of Rotarix lyophilised formulation:
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] and against uncommon rotavirus genotypes G8P[4](severe gastro-enteritis) and G12P[6] (any gastro-enteritis). All of these strains are circulating worldwide.

Protective efficacy in Europe:
A clinical study performed in Europe in 4 000 subjects evaluated ROTARIX given according to different European schedules (2, 3 months; 2, 4 months; 3, 4 months; 3, 5 months).
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 and the two years combined is presented in the following table.

Table: Study conducted in Europe

	1st year of life ROTARIX N=2 572 Placebo N=1 302 (§)	2nd year of life ROTARIX N=2 554 Placebo N=1 294 (§)	1st and 2nd year of life combined ROTARIX N=2 572 Placebo N=1 302 (§)
Vaccine efficacy (%) against any and severe rotavirus gastro-enteritis [95% CI]			

Strain	Any severity	Severe†	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]	89,5* [82,5; 94,1]	96,4* [90,4; 99,1]
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]	58,3* [10,1; 81,0]	85,5* [24,0; 98,5]
G3P[8]	89,9* [9,5; 99,8]	100* [44,8;100]	79,7* [< 0,0; 98,1]	83,1 [<0,0; 99,7]	84,8* [41,0; 97,3]	93,7* [52,8; 99,9]
G4P[8]	88,3* [57,5; 97,9]	100* [64,9; 100]	69,6 [<0,0; 95,3]	87,3* [<0,0; 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]
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]	78,9* [72,7; 83,8]	90,4* [85,1; 94,1]
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]		83,8* [76,8; 88,9]	
Vaccine efficacy (%) against hospitalisation due to rotavirus gastro-enteritis [95 % CI]						
Circulating rotavirus strains	100* [81,8; 100]		92,2* [65,6; 99,1]		96,0* [83,8; 99,5]	

† Severe gastro-enteritis defined as a score ≥ 11 on the Vesikari scale
(§) ATP cohort for efficacy
* 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.

Protective efficacy in Latin America:

A clinical study performed in Latin America in more than 20 000 subjects evaluated ROTARIX ORAL VACCINE given at approximately 2 and 4 months of age.
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) during the first year of life. Protective efficacy of ROTARIX was maintained during the second year of life with an efficacy against severe rotavirus gastro-enteritis of 79,0 % (95 % CI: 66,4; 87,4).
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: 74,5; 100) for Vesikari scores ≥ 19. Enough cases of gastro-enteritis caused by G1P[8] and G9P[8] were observed to demonstrate vaccine efficacy reaching 100 % (95 % CI: > 72,2; 100) for Vesikari scores ≥ 18.
The protective vaccine efficacy observed against severe rotavirus gastro-enteritis is presented in the table below.

Table: Study conducted in Latin America:

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 (%)	Efficacy (%)

	[95 % CI]	[95 % CI]
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]
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]

A pooled analysis of four efficacy studies*, showed a 71,4 % (95 % CI: 20,1; 91,1) efficacy against severe gastro-enteritis (Vesikari score ≥ 11) caused by rotavirus G2P[4] strain.
* In these studies, 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).
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 to dose 2 was 89,8 % (95 % CI: 8,9; 99,8). A pooled analysis of two efficacy studies conducted in Latin America, showed an efficacy against severe rotavirus gastro-enteritis from dose 1 to dose 2 of 64,4 % (95 % CI: 11,9; 86,9).

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 (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 the table below.

Table: Study conducted in Africa:

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

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.
The following 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 [11; 96]
Singapore	< 5 yrs	136/272	All G1P[8]	84 [32; 96] 91 [30; 99]
Taiwan	< 3 yrs	275/1623	All G1P[8]	92 [75; 98] 95 [69; 100]
US	< 2 yrs	85/1062	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	G3P[8]	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	115/1481	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	81/234	All	63 [23;83]

* In subjects who did not receive the full course of vaccination, the effectiveness after one dose was 51 % (95 % CI: 26; 67).
yrs: years
m: months

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.

Pharmacokinetic properties:
Evaluation of pharmacokinetic properties is not required for vaccines.

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

INDICATIONS:
ROTARIX LIQUID ORAL VACCINE is indicated for the prevention of gastro-enteritis caused by Rotavirus.
ROTARIX LIQUID ORAL VACCINE is intended for use in infants in the first six months of life. ROTARIX LIQUID ORAL VACCINE should not be administered to children older than 24 weeks of age.

CONTRA-INDICATIONS:
ROTARIX LIQUID ORAL VACCINE should not be administered to subjects with known hypersensitivity after previous administration of ROTARIX LIQUID ORAL VACCINE or to any component of the vaccine.
ROTARIX LIQUID ORAL VACCINE is contra-indicated in infants who have known or suspected immunodeficiency. However, caution is advised when ROTARIX LIQUID ORAL VACCINE is administered to asymptomatic human immunodeficiency virus (HIV) infected subjects.
Subjects with history of intussusceptions.
Subjects with uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for intussusception.
Subjects with Severe Combined Immunodeficiency (SCID) disorder (see SIDE EFFECTS).

WARNINGS AND SPECIAL PRECAUTIONS:
ROTARIX LIQUID ORAL VACCINE SHOULD UNDER NO CIRCUMSTANCES BE INJECTED.
ROTARIX LIQUID ORAL VACCINE is intended for use in infants in the first six months of life. ROTARIX LIQUID ORAL VACCINE 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.
Administration of ROTARIX LIQUID ORAL VACCINE should be postponed in subjects suffering from acute severe febrile illness. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.
The administration of ROTARIX LIQUID ORAL VACCINE should be postponed in subjects suffering from diarrhoea or vomiting.
There are no data on the safety and efficacy of ROTARIX ORAL VACCINE in infants with gastrointestinal illnesses. Administration of ROTARIX ORAL VACCINE may be considered with caution in such infants when, in the opinion of the physician, withholding the vaccine entails 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.
However, post-marketing safety studies indicate a transient increased incidence of intussusceptions after vaccination, mostly within 7 days of the first dose and to a lesser extent, the second dose. The overall incidence of intussusceptions remains rare. Whether ROTARIX affects the overall risk of intussusceptions 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 intussusceptions, see CONTRA-INDICATIONS.
ROTARIX LIQUID ORAL VACCINE is contra-indicated in infants who have known or suspected immunodeficiency. However, ROTARIX LIQUID ORAL VACCINE can be given to asymptomatic human immunodeficiency virus (HIV) infected subjects.
Administration of ROTARIX in immunosuppressed infants, including infants on immunosuppressive therapy, should be based on careful consideration of potential benefits and risks (see Pharmacodynamic properties).
Do not use ROTARIX vaccines interchangeably with any other rotavirus vaccine.
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.
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 (see Pharmacodynamic properties). 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 after changing child’s nappies).
A protective immune response may not be elicited in all vaccinees.
The extent of protection that ROTARIX might provide against rotavirus strains that have not been circulating in clinical trials is currently unknown (see Pharmacodynamic properties).
ROTARIX LIQUID ORAL VACCINE does not protect against gastro-enteritis due to other pathogens than rotavirus.
ROTARIX LIQUID ORAL VACCINE 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 (HPV), pneumococcal vaccine and meningococcal serogroup C 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 there is currently no evidence that clinical protection against severe rotavirus gastro-enteritis would be affected. The immune response to ROTARIX is unaffected when OPV is administered two weeks apart from ROTARIX.

PREGNANCY AND LACTATION:

ROTARIX LIQUID ORAL VACCINE 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.

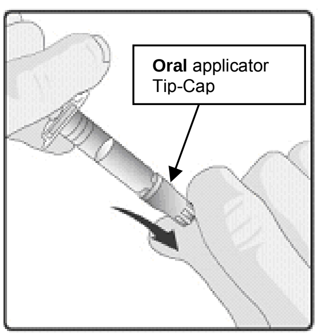
DOSAGE AND DIRECTIONS FOR USE:
The vaccination course consists of two doses. The first dose may be administered from the age of 6 weeks. There should be an interval of at least 4 weeks between doses. The vaccination course should be completed by the age of 24 weeks.
ROTARIX may be given to preterm infants with the same posology (see SIDE EFFECTS and Pharmacodynamic properties).
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 LIQUID ORAL VACCINE complete the 2-dose regimen with ROTARIX LIQUID ORAL VACCINE.

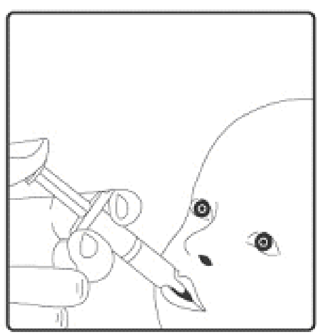
Method of administration:
ROTARIX LIQUID ORAL VACCINE is for oral use only.
ROTARIX LIQUID ORAL VACCINE SHOULD UNDER NO CIRCUMSTANCES BE INJECTED.
There are no restrictions on the infant's consumption of food or liquid, including breast milk, either before or after vaccination.
There is no evidence available to suggest that breastfeeding would reduce the protection against rotavirus gasto-enteritis afforded by ROTARIX LIQUID ORAL VACCINE. Therefore, breastfeeding may be continued during the vaccination schedule.

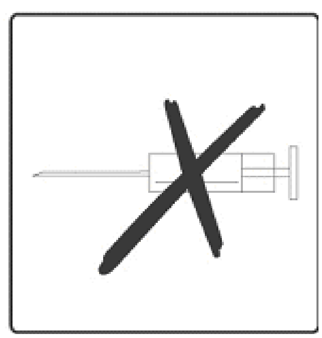
Incompatibilities:
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Instructions for use and handling:
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 in oral applicator:







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

3. Do not inject.

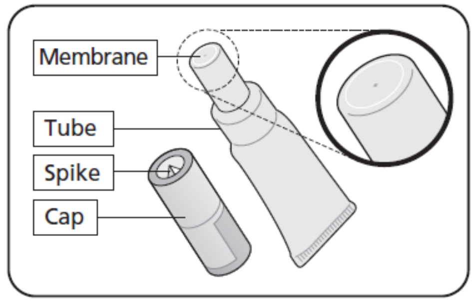
the oral applicator.

Discard the empty oral applicator and tip cap in approved biological waste containers according to local regulations.

Instructions for administration of the vaccine in tube:
Please read the instructions for use all the way through before starting to give the vaccine.

A. What you need to do before giving ROTARIX

- Check the expiry date.
- Check the tube has not been damaged nor is already open.
- Check the liquid is clear and colourless, without any particles in it.



If you notice anything abnormal, do not use the vaccine.

- This vaccine is given orally - straight from the tube.
- It is ready to use - you do not need to mix it with anything.

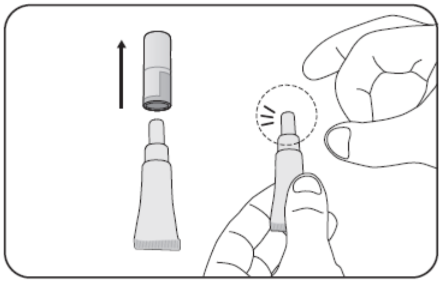
B. Get the tube ready

1. Pull off the cap

- *Keep the cap – you need this to pierce the membrane.*
- *Hold the tube upright.*

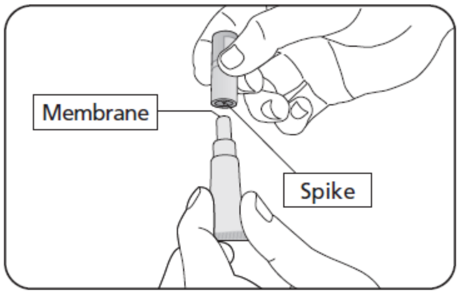
2. Repeatedly flick the top of the tube until it is clear of any liquid

- Clear any liquid from the thinnest section of the tube by flicking just below the membrane.



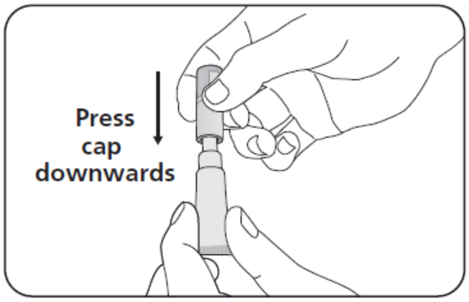
3. Position the cap to open the tube

- Keep the tube held upright.
- Hold the side of tube.
- There is a small spike inside the top of the cap - in the centre.
- Turn the cap upside down (180°).



4. To open the tube

- You do not need to twist. Press the cap down to pierce the membrane.
- Then lift off the cap.



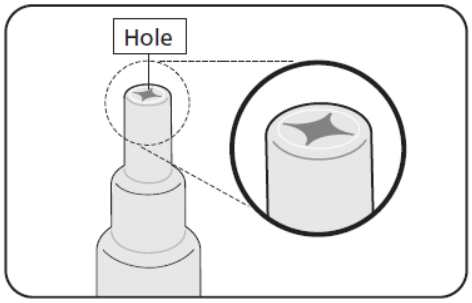
C. Check the tube has opened correctly

1. Check the membrane has been pierced

- There should be a hole at the top of the tube.

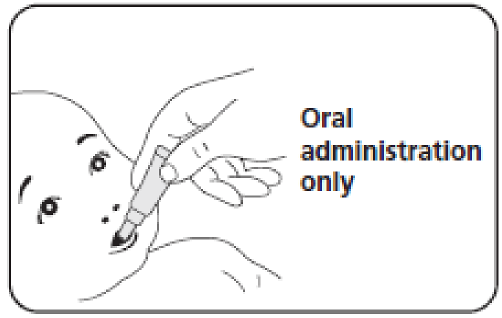
***2.* What to do if the membrane has not been pierced**

- If the membrane has not been pierced return to section B and repeat steps 2, 3 and 4.



D. Give the vaccine

- Once the tube is open check the liquid is clear, without any particles in it.
  If you notice anything abnormal, do not use the vaccine.
- Give the vaccine straight away.



1. Position the child to give the vaccine

- Seat the child leaning slightly backwards.

2. Administer the vaccine

- Squeeze the liquid gently into the side of the child's mouth - towards the inside of their cheek.
- You may need to squeeze the tube a few times to get all of the vaccine out - it is okay if a drop remains in the tip of the tube.

Discard the empty tube and cap in approved biological waste containers according to local regulations.

SIDE EFFECTS:
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 Rotatrix liquid formulation were administered to approximately 1 930 infants. Those trials have shown that the safety and reactogenicity 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 ORAL VACCINE (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 reactions 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 INTERACTIONS), the following adverse events (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 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.

	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, 1 009 preterm infants were administered ROTARIX or placebo (198 were 27-30 weeks gestational age and 801 were 31-36 weeks gestational age). The first dose was administered from 6 weeks after birth. Serious adverse events were observed in 5,1 % of recipients of ROTARIX as compared to 6,8 % of placebo recipients. Similar rates of solicited and unsolicited symptoms were observed in ROTARIX and placebo recipients. No cases of intussusception were reported.

Post Marketing Data:

Gastrointestinal disorders: intussusceptions (see WARNINGS AND SPECIAL PRECAUTIONS), haematochezia, gastroenteritis with vaccine viral shedding in infants with Severe Combined Immunodeficiency (SCID) disorder.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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.

IDENTIFICATION:

ROTARIX LIQUID ORAL VACCINE in oral applicator:
Clear, colourless liquid, free of visible particles in an oral applicator.

ROTARIX LIQUID ORAL VACCINE in tube:
Clear, colourless liquid, free of visible particles in a tube.

PRESENTATION:

ROTARIX LIQUID ORAL VACCINE in oral applicator:
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.
ROTARIX LIQUID ORAL VACCINE in tube:
1,5 ml of oral suspension in a squeezable tube (LDPE) fitted with a membrane and a cap (polypropylene). Pack sizes of 1, 10 or 25.

STORAGE INSTRUCTIONS:

ROTARIX LIQUID ORAL VACCINE in oral applicator:
Store in a refrigerator (2 °C to 8 °C).
Do not freeze.
Protect from light.
Keep out of reach of children.

ROTARIX LIQUID ORAL VACCINE in tube:
Store in a refrigerator (+2 °C to +8 °C).

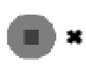
Do not freeze.
Protect from light.
Keep out of reach of children.

For state packs only: The Vaccine Vial Monitor (VVM) is part of the label used for all ROTARIX batches supplied by GlaxoSmithKline Biologicals. The colour dot that appears on the label of the tube is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the tube has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.
The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the tube should be discarded.
It is absolutely critical to ensure that the storage conditions specified above (in particular the cold chain) are complied with. GlaxoSmithKline Biologicals will assume no liability in the event ROTARIX has not been stored in compliance with the storage instructions. Furthermore GlaxoSmithKline Biologicals assumes no responsibility in case a VVM is defective for any reason.

Inner square lighter than outer circle. **If the expiry date has not been passed, USE the vaccine.**

At a later time, inner square still lighter than outer circle. **If the expiry date has not been passed, USE the vaccine.**

Discard point: Inner square matches colour of outer circle. **DO NOT use the vaccine.**



Beyond the discard point: Inner square darker than outer ring. **DO NOT use the vaccine.**

REGISTRATION NUMBER:
43/30.2/0290

NAME AND ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:
GlaxoSmithKline South Africa (Pty) Ltd
39 Hawkins Avenue
Epping Industria 1, 7460

DATE OF THE PUBLICATION OF THE PACKAGE INSERT:
02 June 2017

GDS-14

ROTARIX LIQUID ORAL
Patient Information Leaflet

SCHEDULING STATUS:
S2

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM:
ROTARIX LIQUID ORAL VACCINE
Rotavirus vaccine. Oral suspension.

Read all of this leaflet carefully before your child receives ROTARIX LIQUID ORAL VACCINE.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- **ROTARIX LIQUID ORAL VACCINE** has been prescribed for your child and should not be passed on to others.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

WHAT ROTARIX LIQUID ORAL VACCINE CONTAINS:
One dose (1,5 ml) of ROTARIX contains the live attenuated human rotavirus RIX4414 strain as active substance.
ROTARIX is presented as a suspension for **oral** administration.

The other ingredients in the vaccine are:
Sucrose, di-sodium adipate, Dulbecco's Modified Eagle Medium (DMEM), sterile water.

WHAT ROTARIX LIQUID ORAL VACCINE IS USED FOR:
ROTARIX LIQUID ORAL VACCINE is a vaccine that helps to protect your child against gastro-enteritis (diarrhoea and vomiting) caused by rotavirus infection.
Rotavirus infection is the most common cause of severe diarrhoea in infants and young children. It is easily spread by hand-to-mouth contact with stool from an infected person. Most children with rotavirus diarrhoea recover without any treatment. Some children become very ill with severe vomiting, diarrhoea and life-threatening loss of fluids that requires hospitalization.
When someone is vaccinated, the immune system (the body's natural defence system) will make antibodies against the most commonly occurring types of rotavirus. These antibodies protect against disease caused by these types of rotavirus.
ROTARIX can only protect your child against gastro-enteritis caused by rotavirus.
Vaccination is the best way to protect against these diseases. However, as with all vaccines, ROTARIX may not fully protect all people who are vaccinated.
If your child has recently been vaccinated, it is particularly important to wash your hands after changing the nappy.

BEFORE YOU ARE GIVEN ROTARIX LIQUID ORAL VACCINE:
ROTARIX LIQUID ORAL VACCINE should not be given:

- if your child has previously had any allergic reaction to rotavirus vaccines or any ingredient in ROTARIX. The ingredients in ROTARIX are listed at the beginning of the leaflet. Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.
- if your child was born with a defect of the gastro-intestinal system
- if your child has a rare inherited illness which affects his/her immune system called Severe Combined Immunodeficiency (SCID).

Take special care with ROTARIX LIQUID ORAL VACCINE:

Before your child is vaccinated make sure your doctor knows if any of the following apply:

- if your child has a severe infection with a high temperature. It might be necessary to postpone the vaccination until recovery. A minor infection such as a cold should not be a problem, but talk to your doctor first
- if your child has diarrhoea or is vomiting. It might be necessary to postpone the vaccination until recovery
- if your child suffers from disorders of the stomach or intestines
- if your child has any disease such as HIV infection, which reduces his/her resistance to infection
- if your child is taking any medicine which reduces his/her resistance to infection
- if your child has a close contact such as a household member who has any disease or is taking any medicine which reduces his/her resistance to infection.

After your child has received ROTARIX, contact your doctor/healthcare professional right away if your child experiences severe stomach pain, persistent vomiting, blood in stools, a swollen belly and/or high fever.
As always, please take care to wash your hands thoroughly after changing soiled nappies.

Using ROTARIX LIQUID ORAL VACCINE with food or liquids:
There are no restrictions on taking food or liquids, including breast milk, either before or after vaccination with ROTARIX.

Pregnancy and breastfeeding:
ROTARIX is for use in children only, therefore information on use in pregnancy is not relevant.
Breastfeeding may be continued during the vaccination schedule.

Using other medicines or vaccines with ROTARIX LIQUID ORAL VACCINE:
Always tell your healthcare professional if you are taking any other medicines (this includes complimentary or traditional medicines).
Please tell your doctor if your child is taking or has recently taken any other medicines, including medicines obtained without a prescription or has recently received any other vaccine.
ROTARIX may be given at the same time your child receives other normally recommended vaccines, such as diphtheria, tetanus, whooping cough (pertussis), *Haemophilus influenzae* type b, polio, hepatitis B, pneumococcal and meningococcal vaccines.

HOW TO RECEIVE ROTARIX LIQUID ORAL VACCINE:
Your doctor or nurse will give the recommended dose of ROTARIX LIQUID ORAL VACCINE to your child. The vaccine is always given into the child's mouth.
Under no circumstances should this vaccine be administered by injection.
Your child will receive two doses of the vaccine. The first dose will be given at the earliest at 6 weeks of age. The second dose will be given at least 4 weeks after the first one. The two doses should be given before the age of 24 weeks.
ROTARIX may be given to infants who were born prematurely following the same vaccination course.
If your child spits out or brings back up the vaccine dose, a single replacement dose may be given at the same visit.
It is important that you follow the instructions of your doctor or nurse regarding return visits. If you forget to go back to your doctor at the scheduled time, ask your doctor for advice.

POSSIBLE SIDE EFFECTS:
ROTARIX LIQUID ORAL VACCINE can have some side effects.
Not all side effects reported for ROTARIX LIQUID ORAL VACCINE are included in this leaflet. Should your general health worsen, or if your baby experiences any untoward effects when given this medicine, please consult your doctor, pharmacist, or other healthcare professional for advice.

♦ **Frequent** side effects include:
  - diarrhoea
  - irritability

- **Less frequent** side effects include:
  - flatulence, pain in the stomach
  - dermatitis
- **Other** side effects include:
  - blood in stools
  - children with a rare inherited illness called Severe Combined Immunodeficiency (SCID) may have an inflamed stomach or gut (gastroenteritis) and pass the vaccine virus in their stools. The signs of gastroenteritis may include feeling sick, being sick, stomach cramps or diarrhoea.
  - intussusception (part of the intestine gets blocked or twisted). The signs may include severe stomach pain, persistent vomiting, blood in stools, a swollen belly and/or high fever.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

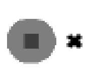
STORING AND DISPOSING OF ROTARIX LIQUID ORAL VACCINE:
DO NOT FREEZE.
The vaccine must be stored at +2 °C to +8 °C (in a refrigerator).
Store in the original package in order to protect from light.
Store all medicines out of reach of children.
Do not use ROTARIX after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

For state packs only: The colour dot that appears on the label of the vaccine tube, is a Vaccine Vial Monitor (VVM). This is a time-temperature sensitive dot that provides an indication of the total amount of heat to which the tube has been exposed. It will warn you when this exposure to heat is likely to have damaged the vaccine, making the vaccine less effective.
Focus on the square inside the ring. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the square is the same colour as the ring or of a darker colour than the ring, then the vaccine should be returned to your doctor or nurse.
It is absolutely critical to ensure that the storage conditions specified above (+2 °C to +8 °C) are followed.

Inner square lighter than outer circle. **If the expiry date has not been passed, USE the vaccine.**

At a later time, inner square still lighter than outer circle. **If the expiry date has not been passed, USE the vaccine.**

Discard point: Inner square matches colour of outer circle. **DO NOT use the vaccine.**



Beyond the discard point: Inner square darker than outer ring. **DO NOT use the vaccine.**

PRESENTATION OF ROTARIX LIQUID ORAL VACCINE:
ROTARIX LIQUID ORAL VACCINE in oral applicator:
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.
ROTARIX LIQUID ORAL VACCINE in tube:
1,5 ml of oral suspension in a squeezable tube (LDPE) fitted with a membrane and a cap (polypropylene). Pack sizes of 1, 10 or 25.

IDENTIFICATION OF ROTARIX LIQUID ORAL VACCINE:
ROTARIX LIQUID ORAL VACCINE is a clear, colourless liquid, free of visible particles, presented in a single dose oral applicator or a single dose tube.

REGISTRATION NUMBER:
43/30.2/0290

NAME AND ADDRESS OF REGISTRATION HOLDER:
GlaxoSmithKline South Africa (Pty) Ltd
39 Hawkins Avenue
Epping Industria 1, 7460

DATE OF PUBLICATION:
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