health

Department:
Health
REPUBLIC OF SOUTH AFRICA

MEDICINES CONTROL COUNCIL
The Registrar of Medicines, Private Bag X828, PRETORIA, 0001
Tel: +27 12 395 8008 *Inquiries*: Ms E Tshabangu or Mr B Malaza
Fax: +27 12 395 9201 *Reference*: 26/7/3/3/0307

The Managing Director
GlaxoSmithkline S.A. (Pty) Ltd
P.O. Box 44
BRYANSTON
7460

Attention: Mrs K. Vermulen

Dear Madam

APPLICATION FOR CERTIFICATE OF A PHARMACEUTICAL PRODUCT

Your application for the above-mentioned certificate refers.

Please find attached the certificate number **26/7/3/3/0307 for** your attention.
Included in this collated document are the following:

(1) The Certificate of a Pharmaceutical Product (CPP);
(2) The English version of the current approved Package Insert & PIL;
(3) The English version of the current approved Container Label (or facsimile);
(4) The formulation of the pharmaceutical product; and
(5) The copy of the registration certificate of the pharmaceutical product.

Please do not hesitate to contact the Inspectorate for any additional clarification.

Yours faithfully

REGISTRAR OF MEDICINES
07/09/2017

DEPT. OF HEALTH

DEPARTMENT OF HEALTH
Republic of South Africa

CERTIFICATE OF A PHARMACEUTICAL PRODUCT

CERTIFICATE NUMBER:	***26/7/3/3/0307***
Exporting (certifying) country:	***REPUBLIC OF SOUTH AFRICA***
Importing (requesting) country:	***MAURITIUS***
1. Name of Product:	***ROTARIX LIQUID ORAL VACCINE***
Dosage form of Product:	***ORAL SUSPENSION***
1.1 Active ingredient(s) and amount(s) per unit dose:	***LIVE ATTENUATED HUMANROTAVIRUS RIX4414 STRAIN not less than 10 $^{6.0}$ $CCID_{50}$***

1.2 Is this product authorised to be placed on the market for use in the exporting country?

(a)	*Yes/No*	***YES***
(b)(I)	*Application pending:*	***NOT APPLICABLE***
(b)(II)	*Right of Sale is currently sanctioned:*	***NOT APPLICABLE***

Details appended of any restriction applied to the sale, distribution or administration of the product that is entered into the conditions under which the product is registered.

1.3 Is this product on the market in the exporting country: ***YES***

- if the answer to 1.2(a) or 1.2(b) is yes, continue with section 2(a) and omit section 2(b);
- if the answer to 1.2(a) or 1.2(b) is no, omit section 2(a) and continue with section 2(b);

2.1.1	*(a)*	*Registration number of product:*	***43/30.2/0290***
	(b)	*Date of Registration:*	***05/03/2009***
	(c)	*Application number of product:*	***NOT APPLICABLE***

2.1.2 Applicant for registration (name and address):

Name of Applicant:
GLAXOSMITHKLINE
S.A. (PTY) LTD

Address of Applicant:
39 HAWKINS AVENUE
EPPING INDUSTRIA 1
CAPE TOWN
7460

2.1.3 Status of Applicant for Registration:

(a)	*Manufactures and packages and labels (total manufacturing):*	***YES***
(b)	*Packages and/or labels a dosage form manufactured by an independent company:*	***NO***
(c)	*Is the applicant involved in any of the above:*	***YES***

DEPT. OF HEALTH

CERTIFICATE NUMBER: 26/7/3/3/0307

3.3	*Do the facilities and operations conform to GMP as recommended by the World Health Organization?*	***N/A***
4.	*Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product: (if no, explain)*	***YES***

Address of certifying authority:

REGISTRAR OF MEDICINES
DEPARTMENT OF HEALTH
PRIVATE BAG X828
PRETORIA
0001
REPUBLIC OF SOUTH AFRICA
+27 012 395-8008
+27 012 395-9201

Telephone number:
Fax Number:

This certificate conforms to the format recommended by the World Health Organization

Name of Authorised person: ***Mr Bafana Malaza***

SIGNATURE

ISSUED DATE: 07TH/09/ 2017

EXPIRY DATE: 07TH/09/2018

DEPT. OF HEALTH
REPUBLIC OF S.A.

OFFICIAL STAMP

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 %

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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 (%) [95 % CI]	Efficacy (%) [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	56,9

	[< 0; 72,3]	[< 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]

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Countries	Age	N (cases/ controls)	Effectiveness after 2 doses RV hospitalisation	
			Strain	Effectiveness (%) [95 % CI]
	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.

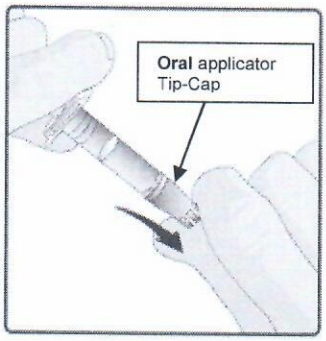
The vaccine is ready to use (no reconstitution or dilution is required).

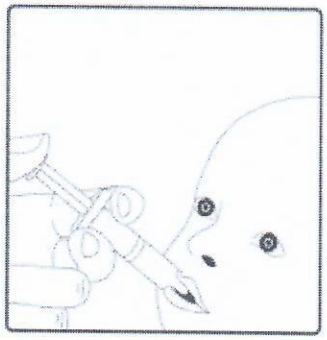
The vaccine is to be administered **orally** without mixing with any other vaccines or solutions.

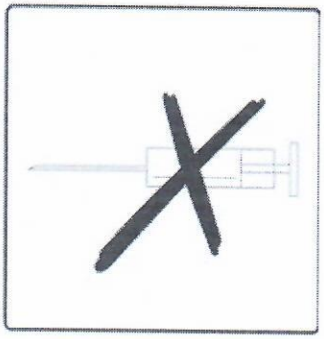
The vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vaccine.

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 the **oral** applicator.
3. **Do not inject.**

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

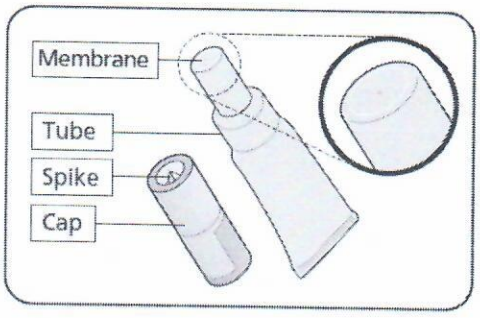
Instructions for administration of the vaccine in tube:

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.

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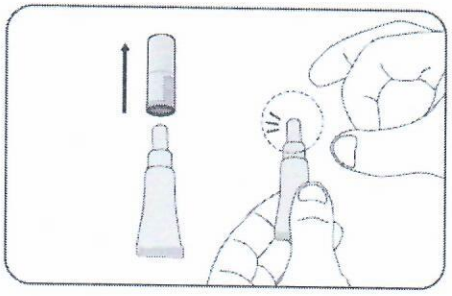
B. Get the tube ready

1. Pull off the cap

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

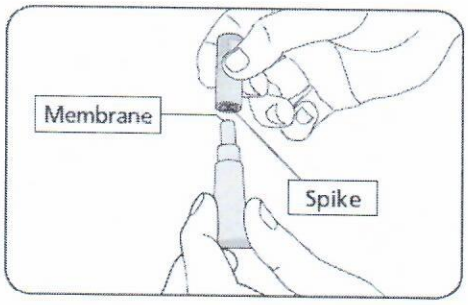


2. Repeatedly flick the top of the tube until it is clear of any liquid

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

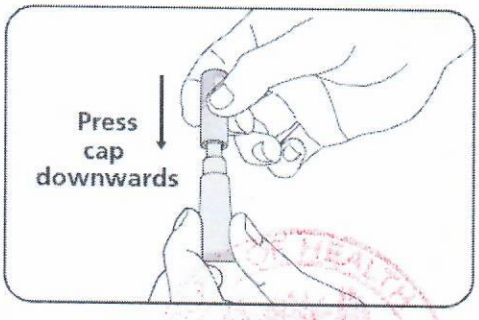
3. Position the cap to open the tube

- 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

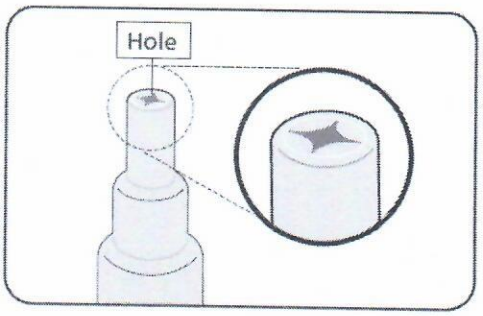
- You do not need to twist. Press the cap down to pierce the membrane.
- Then lift off the cap.



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.



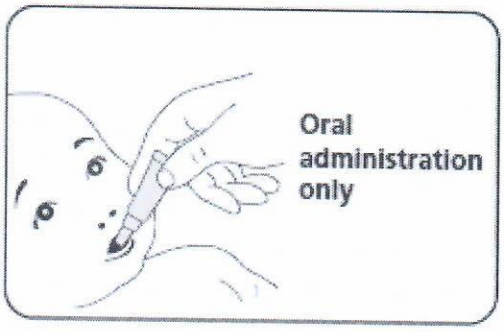
2. What to do if the membrane has not been pierced

- 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

HISTORY:

Submission Date	Details	Response
10 Mar 2009	Compliant PI submitted to MCC.	
31 Dec 2009	Changed to S2, GG 32838.	
29 Jul 2010	Revised dosage schedule.	
26 Apr 2011	Proposed PI for ROTARIX Oral Vaccine 7 September 2006. MCC response 24 May 2010 (Annotated) and safety update.	
17 Aug 2012	Inclusion of VVM information for tender pack only.	Approved 28-10-2013
16 Oct 2012	Response to Bio Recommendations dated 2/3/2012	Approved 15-02-2013. Ratified 24 April 2013
25 Jul 2013	PI updated to bring in line with GDSv10-11	Approved BMC 04-10-2013. Ratified: 08/01/2014
8 May 2013	Safety update to bring in line with GDSv12 and resubmitted 14/07/2015	Not yet evaluated
26 Jan 2016	Change to PE tube (spike design). GDS v013	Approved 31-05-2016
10 Nov 2016	Resubmission of 8-5-2013 (GDSv12) + inclusion of new safety data (GDSv14)	Approved 02 June 2017

HRV liquid vaccine

P.1 Description and Composition
Composition

The Human Rotavirus (HRV) vaccine is a monovalent, live, attenuated virus vaccine derived from the human 89-12 strain which belongs to G1 serotype and [P8] genotype. The parental 89-12 strain was cloned by three end-point dilutions, the selected clone being referred to as RIX4414.

The quantitative composition of the Company's HRV liquid vaccine is provided in Table 1. The volume per nominal dose of the liquid vaccine is 1.5 ml. The liquid preparation is ready-to-use and is to be administered orally.

Table 1 Quantitative composition of the HRV liquid vaccine

Ingredient	Quantity (per nominal dose – 1.5 ml)	Function	Reference to quality standards
Active substance			
Human Rotavirus, Live Attenuated, RIX4414 strain	not less than $10^{6.0}$ $CCID_{50}$	Immunogen	GSK Bio 200292
Excipients			
- Sucrose	1.073 g	Stabiliser	Ph. Eur. 0204
- Di-sodium adipate	132.74 mg	Antacid	Ph. Eur. 1586 (adipic acid) Ph. Eur. 0677 (sodium hydroxyde)
- DMEM[1]	2.26 mg	Bulk diluent	[1]
- Water for Injections q.s. ad	1.5 ml	Solvent	Ph. Eur. 0169

1. Dulbecco's Modified Eagle Medium: prepared in–house with raw materials described in pharmacopoiea and GSK Biologicals' monographs

Pharmaceutical form: ready-to-use liquid vaccine for oral administration
Presentations: pre-filled monodose glass syringes or polyethylene tubes.
Storage conditions: at +2°C/+8°C.
Overage: in order to guarantee the minimum titre of not less than 6.0 log_{10} CCID $_{50}$ per nominal dose required up to the end of shelf-life, the release specification is set at $\geq$ 6.3 log_{10} CCID $_{50}$ per dose.

GW 12/7

DEPARTMENT OF HEALTH

MEDICINE REGISTRATION CERTIFICATE

It is hereby certified that registration of the medicine as described below has been approved by the Medicines Control Council in terms of section 15 (3) (a) of the Medicines and Related Substances Act, 1965 (Act 101 of 1965), subject to the conditions indicated:

This certificate replaces the one issued on: 05/03/2009

1. Registered name **ROTARIX LIQUID ORAL VACCINE**

2. Registration number **43/30.2/0290**

3. Approved name of every active ingredient and quantities thereof per dosage unit or per suitable mass or volume or unit of the medicine
   EACH 1,5 ml DOSE CONTAINS:
   LIVE ATTENUATED HUMAN ROTAVIRUS
   RIX4414 STRAIN not less than $10^{6.0}$ $CCID_{50}$

4. Dosage form **SUSPENSION**

5. Conditions under which the medicine is registered
   see annexure

6. Registered in the name of (applicant)
   GLAXOSMITHKLINE SOUTH AFRICA (PTY) LTD

7. Original date of registration **05/03/2009**

8. Manufacturer, packer, final product release control (FPRC)/final product responsibility (FPRR)
   GLAXOSMITHKLINE BIOLOGICALS S.A., RIXENSART, BELGIUM – MANUFACTURER, FPRC
   GLAXOSMITHKLIN BIOLOGICALS, WAVRE, BELGIUM – MANUFACTURER, PACKER, FPRC
   ***GLAXOSMITHKLINE BIOLOGICALS SAS, SAINT AMAND LES EAUX, FRANCE – PACKER**
   GLAXOSMITHKLINE S.A., EPPING, CAPE TOWN, RSA – PACKER, FPRC, FPRR

*Additional Packer

Issued at Pretoria on

2011 -04- 18

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REGISTRAR OF MEDICINES

DEPT OF HEALTH REPUBLIC OF SA

CERTIFIED A TRUE COPY OF THE ORIGINAL DOCUMENT
2015 -05- 31
BRANCH MANAGER
HOWARD PLACE 7405