Rotarix™
Rotavirus vaccine

QUALITATIVE AND QUANTITATIVE COMPOSITION
1 dose (1.5 ml) contains:
Live attenuated human rotavirus RIX4414 strain not less than $10^{6.0}$ $CCID_{50}$

PHARMACEUTICAL FORM
Oral suspension.
The vaccine is a clear and colourless liquid.

CLINICAL PARTICULARS
Indications
Rotarix™ is indicated for the prevention of gastro-enteritis caused by Rotavirus (*see sections Warnings and Precautions and Pharmacodynamics*).
Dosage and Administration
Posology
The vaccination course consists of two doses. The first dose may be administered from the age of 6 weeks. There should be an interval of at least 4 weeks between doses. The vaccination course should be completed by the age of 24 weeks.
Rotarix™ may be given to preterm infants with the same posology (*see sections Adverse Reactions and Pharmacodynamics*).
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™***.
Method of 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.
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.
For information on instructions for preparation or reconstitution see Use and Handling.

Contraindications
Rotarix™ should not be administered to subjects with known hypersensitivity after previous administration of ***Rotarix™*** vaccine or to any component of the vaccine (*see sections Qualitative and Quantitative Composition and List of Excipients*).
Subjects with history of intussusception.
Subjects with uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose to intussusception.
Subjects with Severe Combined Immunodeficiency (SCID) disorder (*see section Adverse Reactions*).

Warnings and Precautions
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. As with other vaccines, administration of ***Rotarix™*** 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™*** should be postponed in subjects suffering from diarrhoea or vomiting.
There are no data on the safety and efficacy of ***Rotarix™*** in infants with gastrointestinal illnesses.
Administration of ***Rotarix™*** may be considered with caution in such infants when, in the opinion of the physician, withholding the vaccine entails a greater risk.
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 data indicate a transient increased incidence of intussusception in the 31-day period mostly within 7 days following the administration of the first dose of ***Rotarix™***. The overall incidence of intussusception remains rare. Whether ***Rotarix™*** affects the overall risk of intussusception has not been established.
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.
For subjects with a predisposition for intussusception, see Contraindications.
Administration of ***Rotarix™*** in immunosuppressed infants, including infants on immunosuppressive therapy, should be based on careful consideration of potential benefits and risks (*see section Pharmacodynamics*).
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 section Pharmacodynamics*). 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) when changing children's nappies.
As with any vaccine, a protective immune response may not be elicited in all vaccinees (*see section Pharmacodynamics*).
The extent of protection that ***Rotarix™*** might provide against rotavirus strains that have not been circulating in clinical trials is currently unknown (*see section Pharmacodynamics*).
Rotarix™ does not protect against gastro-enteritis due to other pathogens than rotavirus.
ROTARIX™ 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 (HBV), pneumococcal conjugate vaccine and meningococcal serogroup C conjugate vaccine. Clinical studies demonstrated that the immune responses to and the safety profiles of the administered vaccines were unaffected.
Concomitant administration of ***Rotarix™*** and oral polio vaccine (OPV) does not affect the immune response to the polio antigens. Although concomitant administration of OPV may slightly reduce the immune response to rotavirus vaccine, clinical protection against severe rotavirus gastro-enteritis was shown to be maintained.
Pregnancy and Lactation
Rotarix™ 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.
Effects on Ability to Drive and Use Machines
Rotarix™ is not intended for use in adults.
Adverse Reactions
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 ≥1/1000 and <1/100
Rare ≥1/10,000 and <1/1000
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 ***Rotarix™*** liquid formulation were administered to approximately 1,900 infants. Those trials have shown that the safety profile of the liquid formulation is comparable to the lyophilised formulation.
In a total of twenty-three clinical trials, approximately 106,000 doses of ***Rotarix™*** (lyophilised or liquid formulation) were administered to approximately 51,000 infants.
In three placebo-controlled clinical trials, in which ***Rotarix™*** was administered alone (administration of routine paediatric vaccines was staggered, the incidence and severity of the solicited events (collected 8 days post-vaccination), diarrhoea, vomiting, loss of appetite, fever irritability and cough/runny nose, were not significantly different in the group receiving ***Rotarix™*** when compared to the group receiving placebo. No increase in the incidence or severity of these events was seen with the second dose.
In a pooled analysis from seventeen placebo-controlled clinical trials including trials in which ***Rotarix™*** was co-administered with routine paediatric vaccines (*see section Interactions*), the following adverse reactions (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 subjects were enrolled. This trial gave evidence of no increased risk of intussusception in the ***Rotarix™*** group when compared with the placebo group as shown in the table below.

	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 to 6.8% of placebo recipients. Similar rates of other adverse events were observed in ***Rotarix™*** and placebo recipients. No cases of intussusception were reported.
Post-marketing data
Gastrointestinal disorders:
Rare: intussusception, (*see section Warnings and Precautions*) haematochezia, gastroenteritis with vaccine viral shedding in infants with Severe Combined Immunodeficiency (SCID) disorder.
Overdose
Insufficient data are available.

PHARMACOLOGICAL PROPERTIES
Pharmaco-therapeutic group: viral vaccines, ATC code: J07BH01
Pharmacodynamics
Protective efficacy
The protective efficacy of ***Rotarix™*** lyophilised formulation against any and severe rotavirus gastro-enteritis was evaluated in Europe, Latin America, Africa and Asia.
Severity of gastro-enteritis was defined according to two different criteria:

- the Vesikari 20-point scale, which evaluates the full clinical picture of rotavirus gastro-enteritis by taking into account the severity and duration of diarrhoea and vomiting, the severity of fever and dehydration as well as the need for treatment
or
- the clinical case definition based on World Health Organization (WHO) criteria

Protective efficacy in Europe and Latin America
After two doses of ***Rotarix™***, the protective vaccine efficacy observed in the studies conducted in Europe and Latin America during the first and second year of life combined is presented in table 1 and table 2.

Table 1: Study conducted in Europe: 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†**
G1P[8]	89.5 [82.5;94.1]	96.4 [90.4;99.1]
G2P[4]	58.3 [10.1;81.0]	85.5 [24.0;98.5]
G3P[8]	84.8 [41.0;97.3]	93.7 [52.8;99.9]
G4P[8]	83.1 [55.6;94.5]	95.4 [68.3;99.9]
G9P[8]	72.5 [58.6;82.0]	84.7 [71.0;92.4]
Strains with P[8] genotype	81.8 [75.8; 86.5]	91.9 [86.8;95.3]
Circulating rotavirus strains	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	83.8 [76.8;88.9]	
Vaccine efficacy (%) against hospitalisation due to rotavirus gastro-enteritis [95% CI]		
Circulating rotavirus strains	96.0 [83.8;99.5]	

† Severe gastro-enteritis was defined as a score ≥11 on the Vesikari scale
(§) ATP cohort for efficacy. This includes all subjects from the ATP cohort for safety who have entered into the concerned efficacy follow-up period

Table 2: Study conducted in Latin America: 1st and 2nd year of life combined (*Rotarix™* N=7205; Placebo N=7081(§))

Strain	**Vaccine efficacy (%) against severe rotavirus gastro-enteritis† [95% CI]**
All RVGE	80.5 [71.3; 87.1]
G1P[8]	82.1 [64.6;91.9]
G3P[8]	78.9 [24.5;96.1]
G4P[8]	61.8 [4.1;86.5]
G9P[8]	86.6 [73.0;94.1]
Strains with P[8] genotype	82.2 [73.0;88.6]

† Severe rotavirus gastro-enteritis was defined as an episode of diarrhoea with or without vomiting that required hospitalisation/efficacy. Trying re-hydration therapy in a medical facility (WHO criteria)
(§) ATP cohort for efficacy. This includes all subjects from the ATP cohort for safety who have entered into the concerned efficacy follow-up period
The vaccine efficacy against severe rotavirus gastro-enteritis was 38.6% (95% CI: <0.0;84.2) for G2P[4] strain. The number of cases, on which the estimates of efficacy against G2P[4] were based, were very small.
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.
Since 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, the levels of vaccine efficacy observed with the lyophilised formulation can be extrapolated to the liquid formulation.

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 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: Study conducted in Africa: 1st year of life – pooled results (*Rotarix™* N=2,974; Placebo N = 1,443 (§))

Vaccine efficacy (%) against any rotavirus gastro-enteritis [95% CI]		
Strain	**Any severity**	**Severe**
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)**

† Severe gastro-enteritis was defined as a score ≥11 on the Vesikari scale
(§) ATP cohort for efficacy. This includes all subjects from the ATP cohort for safety who have entered into the concerned efficacy follow-up period
* Not statistically significant (p ≥ 0.05). These data should be interpreted with caution

Sustained efficacy up to 3 years of age in Asia
A clinical study conducted in Asia (Hong Kong, Singapore and Taiwan) in more than 10000 subjects evaluated ***Rotarix™*** given according to different schedules (2, 4 months of age; 3, 4 months of age). After two doses of ***Rotarix™***, the protective vaccine efficacy observed up to 3 years of age is presented in table 4.

Table 4 : Study conducted in Asia: Efficacy up to 2 and 3 years of age (*Rotarix™* N=5263; Placebo N = 5256 (§))

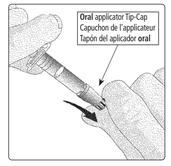
	Efficacy up to 2 years of age	**Efficacy up to 3 years of age**
Vaccine efficacy (%) against severe rotavirus gastro-enteritis (95% CI)		
Strain	**Severe†**	**Severe†**
G1P[8]	100.0 (80.8;100.0)	100.0 (84.8;100.0)
G2P[4]	100.0* (<0;100.0)	100.0* (<0;100.0)
G3P[8]	94.5 (64.9;99.9)	95.2 (70.4;99.9)
G9P[8]	91.7 (43.8;99.8)	91.7 (43.8;99.8)
Strains with P[8] genotype	95.8 (83.8;99.5)	96.6 (87.0;99.6)
Circulating rotavirus strains	96.1 (85.1;99.5)	96.9 (88.3;99.6)
Vaccine efficacy (%) against rotavirus gastro-enteritis requiring hospitalisation and/or rehydration therapy in a medical facility [95% CI]		
Circulating rotavirus strains	94.2 (82.2;98.8)	95.5 (86.4;99.1)

† Severe gastro-enteritis was defined as a score ≥11 on the Vesikari scale
(§) ATP cohort for efficacy. This includes all subjects from the ATP cohort for safety who have entered into the concerned efficacy follow-up period
* Not statistically significant (p ≥ 0.05). These data should be interpreted with caution

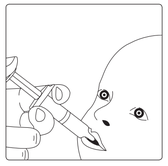
Immune response
In different clinical studies conducted in Europe, Latin America and Asia, 1,957 infants received ***Rotarix™*** lyophilised formulation and 1,006 infants received a placebo according to different vaccination schedules. The percentage of subjects initially seronegative for rotavirus (IgA antibody titres <20 U/ml (by ELISA)) with serum anti-rotavirus IgA antibody titers ≥ 20U/ml one or two months after the second dose of vaccine or placebo ranges from 77.9% to 100% and from 0% to 17.1% respectively.
In three comparative trials, the immune response elicited by ***Rotarix™*** liquid formulation was comparable to the one elicited by ***Rotarix™*** lyophilized formulation.
In a clinical study conducted in Africa, the immune response was evaluated in 332 infants who received ***Rotarix™*** (N=221) or placebo (N=111) according to a 10 and 14 weeks schedule (2 doses) or 6, 10 and 14 weeks schedule (3 doses). The percentage of subjects initially seronegative for rotavirus (IgA antibody titres < 20 U/ml (by ELISA)) with serum anti-rotavirus IGA antibody titers ≥ 20 U/ml one month after the last dose of vaccine or placebo was 58.4% (pooled regimens) and 22.5%, respectively.
Immune response in preterm infants
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 ≥ 20U/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™*** lyophilised formulation or placebo. The safety profile was similar between ***Rotarix™*** and placebo recipients.
Vaccine shedding
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.
Pharmacokinetics
Evaluation of pharmacokinetic properties is not required for vaccines.
Clinical Studies
See "Pharmacodynamics"
Pre-clinical Safety Data
Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity.

PHARMACEUTICAL PARTICULARS
List of Excipients
Sucrose, Di-sodium Adipate, Dulbecco's Modified Eagle Medium (DMEM), Sterile water.
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.
Incompatibilities
This medicinal product must not be mixed with other medicinal products.
Shelf Life
The expiry date of the vaccine is indicated on the label and packaging.
Special Precautions for Storage
Store in a refrigerator (2°C – 8°C). Do not freeze.
Store in the original package in order to protect from light.
Nature and Contents of Container
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.
Instructions for Use/ Handling (see end of the leaflet)
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: / Instructions pour l'administration du vaccin: / Instrucciones para la administración de la vacuna:



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.

International Product Information version GDS010IPI07 (22/06/2011)
©2011/2012 GlaxoSmithKline group of companies

Manufacturer/Fabricant/Fabricante:
GlaxoSmithKline Biologicals s.a. Rue de l'Institut 89, B-1330 Rixensart, Belgium.
Tel: (32.2) 656 81 11 Fax: (32.2) 656 80 00

Not all presentations are available in every country.

Rotarix is a trademark of the GlaxoSmithKline group of companies

Rotarix™
GlaxoSmithKline