ROTARIX® PRODUCT INFORMATION

Rotavirus Vaccine, live attenuated

NAME OF THE MEDICINE

ROTARIX, powder and solvent for suspension for oral administration
Rotavirus vaccine

DESCRIPTION

ROTARIX is a lyophilised preparation of the live attenuated RIX4414 strain of human rotavirus of the G1P[8] type (derived from the 89-12 strain). The virus strain is obtained by propagation on a well-characterised Vero cell line.

ROTARIX is presented as a white powder for reconstitution with a separately supplied calcium carbonate buffer solvent. The solvent is presented as a turbid liquid with a slow settling white deposit and a colourless supernatant.

Each 1 mL dose of the reconstituted vaccine contains not less than $10^{6.0}$ $CCID_{50}$ (cell culture infectious dose 50%) of the RIX 4414 strain of human rotavirus. The vaccine also contains sucrose, dextran 40, sorbitol, amino acids, Dulbecco's Modified Eagle Medium, calcium carbonate, xanthan gum and water for injections.

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

CLINICAL PHARMACOLOGY

ROTARIX is an attenuated human rotavirus vaccine that induces protective immunity against human rotavirus gastro-enteritis and its complications (dehydration, physician visits and hospitalisations).

CLINICAL TRIALS

Clinical studies have been conducted in Finland and Latin America to evaluate the protective efficacy of *ROTARIX* against any and severe rotavirus gastro-enteritis. Protective efficacy has been shown to be higher against severe rotavirus gastroenteritis than rotavirus gastroenteritis of any severity. Protective efficacy has been demonstrated against rotavirus of types G1P[8], G3P[8] and G9P[8].

A clinical study performed in Finland evaluated a formulation with a lower viral titre ($10^{5.3}$ CCID50/dose) than the commercial formulation in approximately 400 subjects. Severity of gastro-enteritis was defined according to the Vesikari 20-point scale which evaluates the full clinical picture of rotavirus gastro-enteritis by taking into account the severity and duration of diarrhoea and vomiting, the severity of fever and dehydration as well as the need for treatment. The first dose was given between 6 and 12 weeks of age and the second dose was administered 4 to 8 weeks later. After two doses of *ROTARIX*, the protective vaccine efficacy during the first year of life was 90% (95% CI: 10.3; 99.8) against severe gastro-enteritis (Vesikari score ≥11) and 73% (95% CI: 27.1; 90.9) against any rotavirus gastro-enteritis. Protective efficacy of *ROTARIX* during the second year of life was 83% (95% CI: 7.2; 98.4) and 73% (95% CI: 19.9; 91.8) against severe and any gastro-enteritis respectively. The type specific vaccine efficacy observed against severe gastro-enteritis (Vesikari score ≥11) caused by G1P[8] was 87% (95% CI: 24.8; 99.7) and against any gastro-enteritis caused by G1P[8] was 68% (95% CI: 9.8; 89.5).

A clinical study performed in Latin America evaluated the commercial formulation (viral titre of $10^{6.5}$ $CCID_{50}$/dose) in more than 20,000 subjects. The first dose was given between 6 and 12 weeks of age and the second dose was administered 4 to 8 weeks later. The observed vaccine efficacy against severe rotavirus gastro-enteritis requiring hospitalisation and/or rehydration therapy in a medical facility is shown in the following table:

Table: Efficacy of *ROTARIX* against severe rotavirus gastroenteritis from 2 weeks after Dose 2 up to the end of the first year follow-up – Latin American study

Group	Vaccine Efficacy	95%CI
All circulating wild type	84.7%	71.7% - 92.4%
G1P[8]	91.8%	74.1% - 98.4%
G3P[8]	87.7%	8.3% - 99.7%
G9P[8]	90.6%	61.7% - 98.9%
G2P[4]	41.0%	-79.2% - 82.4%
All strains with P8 genotype	90.9%	79.2% - 96.8%

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

INDICATIONS

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

CONTRAINDICATIONS

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

ROTARIX should not be administered to subjects with any history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract.

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

PRECAUTIONS

***ROTARIX* should under no circumstances be injected.**

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

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.

The safety of *ROTARIX* has not been established in subjects with primary and secondary immunodeficiency states.

ROTARIX vaccine antigen is excreted in stools by more than half of recipients after the first vaccine dose. There is potential for transmission to non-vaccinated contacts. *ROTARIX* should be administered with caution to infants with close contacts who are immunodeficient, such as household members who are immunocompromised or receiving immunosuppressive therapy. Contacts of recent vaccinees should be advised to observe personal hygiene (e.g. wash their hands after changing child's nappies).

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

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

Carcinogenicity and Mutagenicity

ROTARIX has not been evaluated for carcinogenicity or mutagenicity.

Impairment of Fertility

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

Genotoxicity

ROTARIX has not been evaluated for genotoxicity.

Use in Pregnancy (Category B2):

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

Use in Lactation:

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

Paediatric Use

ROTARIX is intended for use in infants in the first six months of life. *ROTARIX* should not be administered to children older than 6 months of age as safety has not been demonstrated, particularly in relation to risk of intussusception.

Use in the Elderly

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

Interactions

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

Clinical studies, involving more than 2,000 subjects, were performed where *ROTARIX* and oral polio vaccine (OPV) were administered two weeks apart. The immune response to *ROTARIX* and OPV was unaffected. In three immunogenicity studies, involving approximately 1,200

subjects, *ROTARIX* was concomitantly administered with OPV. The immune response to OPV, as well as the response to *ROTARIX* after the second dose, were unaffected. *ROTARIX* can be concomitantly administered with OPV if this is in accordance with local recommendations. In the absence of local recommendations, an interval of two weeks between the administration of OPV and *ROTARIX* should be respected.

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

Effects on laboratory tests
ROTARIX has not been evaluated for effects on laboratory tests.

ADVERSE REACTIONS

Clinical Trial Experience

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

In two clinical trials (Finland), *ROTARIX* was administered alone (administration of routine paediatric vaccines was staggered). The incidence of diarrhoea, fever and irritability was not different in the group receiving *ROTARIX* when compared to the control group receiving placebo. No increase in the incidence or severity of these events was seen with the second dose.

In the other nine clinical trials, *ROTARIX* was co-administered with other paediatric vaccines (see Interactions). The adverse reaction profile observed in these subjects was similar to the adverse reaction profile observed in subjects receiving the same paediatric vaccines and placebo.

Adverse reactions per system organ class and frequency within a maximum of 43 days after vaccination

System Organ Class	Preferred term	Incidence in the Rotarix group (%)	Incidence in the placebo group (%)
Infections and infestations	upper respiratory tract infection	0.09	0.06
Psychiatric disorders	irritability	45.8	41.8
	crying	0.39	0.52
	sleep disorder	0.39	0.52
Nervous system disorders	somnolence	0.39	0.00
Respiratory, thoracic and	hoarseness	0.02	0.00
mediastinal disorders	rhinorrhoea	0.02	0.00
Gastrointestinal disorders	loss of appetite	15.9	11.5
	diarrhoea	5.1	3.4
	vomiting	8.5	9.7
	flatulence	2.07	0.78
	abdominal pain	1.3	0.52
	regurgitation of food	2.20	1.55
	constipation	0.52	0.00
Skin and subcutaneous tissue	dermatitis	0.06	0.03
disorders	rash	0.04	0.03
Musculoskeletal and connective tissue disorders	muscle cramp	0.02	0.00
General disorders and	fever*	9.2	6.8
administration site conditions	fatigue	1.30	2.58

*rectal temperature >38˚C

The risk of intussusception has been evaluated in a large safety trial conducted in Latin America and Finland where 63,225 subjects were enrolled. This trial gave evidence of no increased risk of intussusception in the *ROTARIX* group when compared with the placebo group as shown in the table below.

Intussusception within 31 days after administration of:	ROTARIX N = 31,673	Placebo N = 31,552	Relative risk (95% CI)
First dose	1	2	0.50 (0.07; 3.80)
Second dose	5	5	0.99 (0.31; 3.21)

Post-marketing data

There are currently no post-marketing surveillance data available for *ROTARIX.*

DOSAGE AND ADMINISTRATION

Dosage

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

Repeat dosing is not indicated if an infant should spit out, regurgitate or vomit during or after the administration of the vaccine. The vaccination course should be completed as recommended above.

Administration

ROTARIX is for oral use only.

ROTARIX SHOULD UNDER NO CIRCUMSTANCES BE INJECTED.

There are no restrictions on the infant's consumption of food or liquid, including breast milk, either before or after vaccination.

Instructions for use and handling

A white deposit and clear supernatant is observed upon storage of the syringe containing the solvent. The content of the syringe should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to administration.

The vaccine is for single use only. Any unused vaccine or waste material should be disposed of in accordance with local requirements.

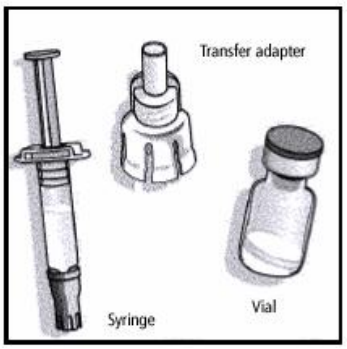
The reconstituted vaccine should also be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, discard the vaccine.

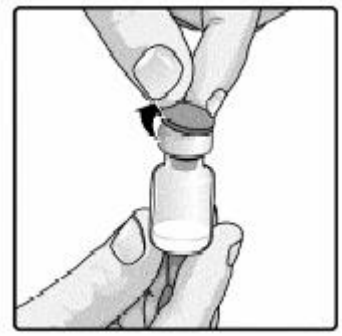
Reconstitution instructions:

1. Remove the plastic cover from the vial containing the powder.

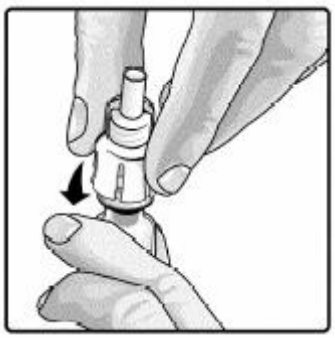
2. Connect the transfer adapter onto the vial by pushing it downwards until the transfer adapter is properly and solidly placed.
3. Shake the syringe containing the solvent vigorously. The shaken suspension will appear as a turbid liquid with a slow settling white deposit.
4. Remove the stopper from the syringe.
5. Connect the syringe onto the transfer adapter by pushing it.
6. Inject the entire contents of the syringe into the vial containing the powder.
7. Shake the vial and examine for complete dissolution. The reconstituted vaccine will appear more turbid than the suspension alone. This appearance is normal.
8. Withdraw the entire mixture back into the syringe.
9. Remove the syringe from the transfer adapter.
10. Administer the entire content of the syringe **ORALLY** (on the inside of the cheek). The child should be seated in a reclining position. **Do not inject.**

If the vaccine is not administered immediately, the syringe containing the reconstituted vaccine should be shaken gently again before **ORAL** administration. **Do not inject.**



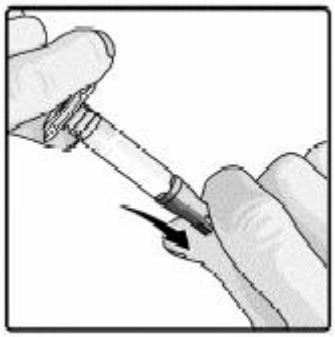


1. Remove the plastic cover from the vial containing the lyophilised powder.

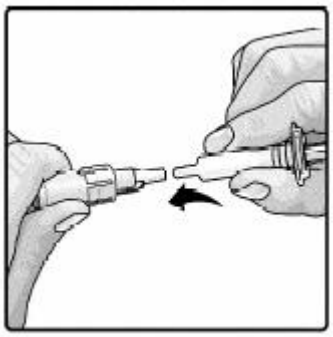


2. Connect the transfer adapter onto the vial by pushing it downwards until the transfer adapter is properly and solidly placed.

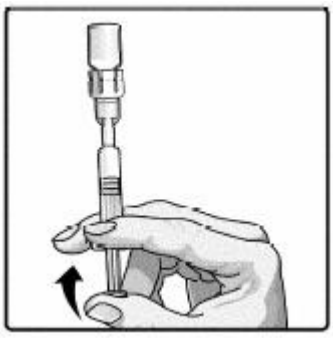
3. Shake the syringe containing the suspension vigorously.
The shaked suspension will appear as a turbid liquid with a slow settling white deposit.



4. Remove the stopper from the syringe.



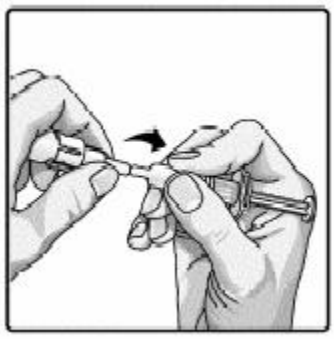
5. Connect the syringe onto the transfer adapter by pushing it.



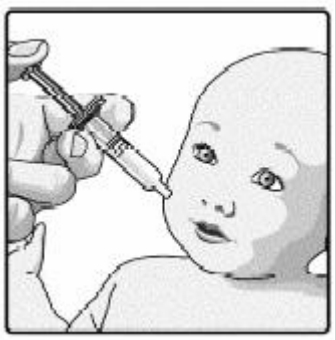
6. Inject the entire contents of the syringe into the vial containing the lyophilised powder.

7. Shake the vial and examine for complete dissolution.
The reconstituted vaccine will appear more turbid than the suspension alone. This appearance is normal.

8. Withdraw the entire mixture back into the syringe.



9. Remove the syringe from the transfer adapter.



10. Administer the entire content of the syringe orally (on the inside of the cheek). The child should be seated in a reclining position. Do not inject.

OVERDOSAGE

No case of overdose has been reported.

PRESENTATION AND STORAGE CONDITIONS

Powder in glass vial (Type I, Ph. Eur.) with stopper (butyl rubber).
Solvent (1 mL) in glass pre-filled syringe (Type I, Ph. Eur.) with a plunger stopper (butyl rubber).
Transfer adapter for reconstitution.
Pack size of 1.

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

Before reconstitution:
The solvent may be stored at either 2°C to 8°C or at ambient temperature (the storage temperature must not exceed 37°C).

Experimental data show that the powder is stable when stored at 37°C for 1 week. However, these data are not recommendations for storage.

After reconstitution:
After reconstitution, the vaccine should be administered promptly or kept in the refrigerator (2°C to 8°C). If it is not used within 24 hours, it should be discarded.

Experimental data show that the reconstituted vaccine could also be kept to 24 hours at ambient temperature (18°C to 25°C). However, these data are not recommendations for storage.

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POISON SCHEDULE OF THE DRUG
Schedule 4.

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