WHO LEAFLET

DESCRIPTION

Rotarix **oral** suspension
Rotavirus vaccine, live

1 dose (1.5 mL) contains:
Human rotavirus RIX4414 strain (live, attenuated)* not less than $10^{6.0}$ $CCID_{50}$
*Produced on Vero cells

Excipients: Sucrose, Di-sodium Adipate, Dulbecco's Modified Eagle Medium (DMEM) (containing phenylalanine, sodium, glucose, and other substances), sterile water.

Excipients with known effect: This product contains 1 073 mg of sucrose, 32 mg of sodium, 10 micrograms of glucose and 0.15 microgram of phenylalanine per dose (see section *Precautions*).

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.

ADMINISTRATION

Rotarix is for **oral** use only.
ROTARIX SHOULD UNDER NO CIRCUMSTANCES BE INJECTED.

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 medicinal product or waste material should be disposed of in accordance with local requirements.

Instructions for administration of the vaccine:
Please read the instructions for use all the way through before starting to give the vaccine **(see pictograms and related text provided before the VVM section).**

IMMUNISATION SCHEDULE

Rotarix is indicated for the active immunisation of infants aged 6 to 24 weeks for prevention of gastro-enteritis due to rotavirus infection (see sections *Precautions* and *Pharmacological properties*).
The use of Rotarix should be based on official recommendations.

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 preferably be given before 16 weeks of age, but must be completed by the age of 24 weeks.

Rotarix may be given with the same posology to preterm infants born after at least 27 weeks of gestational age (see sections *Side effects* and *Pharmacological 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 recommended that infants who receive a first dose of Rotarix complete the 2-dose regimen with

Rotarix. There are no data on safety, immunogenicity or efficacy when Rotarix is administered for the first dose and another rotavirus vaccine is administered for the second dose or vice versa.

Paediatric population
Rotarix should not be used in children over 24 weeks of age.

Use with other vaccines
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 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 in a clinical trial involving more than 4 200 subjects who received Rotarix concomitantly with OPV.

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

SIDE EFFECTS

Summary of the safety profile
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 (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 events 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 section *Immunisation schedule*), the following adverse reactions (collected 31 days post-vaccination) were considered as possibly related to vaccination.

Tabulated list of adverse reactions
Adverse reactions reported are listed according to the following frequency:

Frequencies are reported as:

Very common	(≥ 1/10)
Common	(≥ 1/100 to < 1/10)
Uncommon	(≥ 1/1 000 to < 1/100)
Rare	(≥ 1/10 000 to < 1/1 000)
Very rare	(< 1/10 000)

System Organ Class	Frequency	Adverse reactions
Gastrointestinal disorders	Common	Diarrhoea
	Uncommon	Abdominal pain, flatulence
	Very rare	Intussusception (see section *Precautions*)
	Not known*	Haematochezia
	Not known*	Gastroenteritis with vaccine viral shedding in infants with Severe Combined Immunodeficiency (SCID) disorder
Skin and subcutaneous tissue disorders	Uncommon	Dermatitis
	Very rare	Urticaria
General disorders and administration site conditions	Common	Irritability
Respiratory, thoracic and mediastinal disorders	Not known*	Apnoea in very premature infants (≤ 28 weeks of gestation) (see section *Precautions*)

*Because these events were reported spontaneously, it is not possible to reliably estimate their frequency.

Description of selected adverse reactions

Intussusception
Data from observational safety studies performed in several countries indicate that rotavirus vaccines carry an increased risk of intussusception, mostly within 7 days of vaccination. Up to 6 additional cases per 100 000 infants have been observed in these countries against a background incidence of 25 to 101 per 100 000 infants (less than one year of age) per year, respectively.
There is limited evidence of a smaller increased risk following the second dose.
It remains unclear whether rotavirus vaccines affect the overall incidence of intussusception based on longer periods of follow-up (see section *Precautions*).

Other special populations

Safety in preterm infants
In a clinical study, 670 pre-term infants from 27 to 36 weeks of gestational age were administered Rotarix lyophilised formulation and 339 received placebo. The first dose was administered from 6 weeks after birth. Serious adverse events were observed in 5.1% of recipients of Rotarix as compared with 6.8% of placebo recipients. Similar rates of other adverse events were observed in Rotarix and placebo recipients. No cases of intussusception were reported.

Safety in infants with human immunodeficiency (HIV) infection
In a clinical study, 100 infants with HIV infection were administered Rotarix lyophilised formulation or placebo. The safety profile was similar between Rotarix and placebo recipients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section *Description*.
Hypersensitivity after previous administration of rotavirus vaccines.
History of intussusception.
Subjects with uncorrected congenital malformation of the gastrointestinal tract that would predispose for intussusception.

Subjects with Severe Combined Immunodeficiency (SCID) disorder (see section *Side effects*).

Administration of Rotarix should be postponed in subjects suffering from acute severe febrile illness.
The presence of a minor infection is not a contraindication for immunisation.
The administration of Rotarix should be postponed in subjects suffering from diarrhoea or vomiting.

PRECAUTIONS

It is good clinical practice that vaccination should be preceded by a review of the medical history especially with regard to the contraindications and by a clinical examination.

There are no data on the safety and efficacy of Rotarix in infants with gastrointestinal illnesses or growth retardation. 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.

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) since data from observational safety studies indicate an increased risk of intussusception, mostly within 7 days after rotavirus vaccination (see section *Side effects*). Parents/guardians should be advised to promptly report such symptoms to their healthcare provider.

For subjects with a predisposition for intussusception, see section *Contraindications*.

Asymptomatic and mildly symptomatic HIV infections are not expected to affect the safety or efficacy of Rotarix. A clinical study in a limited number of asymptomatic or mildly symptomatic HIV positive infants showed no apparent safety problems (see section *Side effects*).
Administration of Rotarix to infants who have known or suspected immunodeficiency, including *in utero* exposure to an immunosuppressive treatment, should be based on careful consideration of potential benefits and risks.

Excretion of the vaccine virus in the stools is known to occur 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 of Rotarix lyophilised formulation and 4% of stools after the second dose. When these stools were tested for the presence of live vaccine strain, only 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.
Cases of transmission of this excreted vaccine virus to seronegative contacts of vaccinees have been observed without causing any clinical symptom.

Rotarix should be administered with caution to individuals with immunodeficient close contacts, such as individuals with malignancies, or who are otherwise immunocompromised or individuals receiving immunosuppressive therapy.

Contacts of recent vaccinees should observe personal hygiene (e.g. wash their hands after changing child’s nappies).

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity.
As the benefit of the vaccination is high in this group of infants, vaccination should not be withheld or delayed.

A protective immune response may not be elicited in all vaccinees (see section *Pharmacological properties*).
The extent of protection that Rotarix might provide against other rotavirus strains that have not been circulating in clinical trials is currently unknown. Clinical studies from which efficacy data were derived were conducted in Europe, Central, South America, Africa and Asia (see section *Pharmacological properties*).

Rotarix does not protect against gastro-enteritis due to other pathogens than rotavirus.
No data are available on the use of Rotarix for post-exposure prophylaxis.

ROTARIX SHOULD UNDER NO CIRCUMSTANCES BE INJECTED.

This vaccine contains sucrose and glucose as excipients. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this vaccine.
This vaccine contains 0.15 microgram phenylalanine in each dose. Phenylalanine may be harmful for patients with phenylketonuria (PKU).
This vaccine contains 32 mg sodium in each dose.

Pregnancy and lactation
Rotarix is not intended for use in adults. There are no data on the use of Rotarix during pregnancy and lactation.

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.

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

Overdose
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.

Incompatibilities
This medicinal product must not be mixed with other medicinal products.

PHARMACOLOGICAL PROPERTIES

For this section see WHO Product Information on the WHO website

STORAGE

The expiry date of the vaccine is indicated on the label and packaging.
The vaccine should be used immediately after opening.

Store in a refrigerator (2°C – 8°C). Freezing is not recommended for storage. Nevertheless if the vaccine has been accidentally stored for a maximum of 12 hours at -20°C, stability data generated indicate that the vaccine retains its potency.

Store in the original package, in order to protect from light.

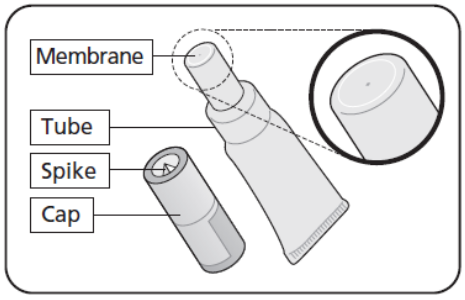
PRESENTATION

1.5 mL of **oral** suspension in a squeezable tube (polyethylene) fitted with a membrane and a tube cap (polypropylene) in pack sizes of 1, 10 or 50. Not all pack sizes may be marketed.

Instructions for administration of the vaccine:

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

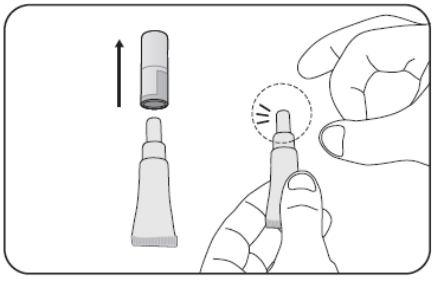


- Check the expiry date.
- Check the tube has not been damaged nor is already open.
- Check the liquid is clear and colourless, without any particles in it.

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

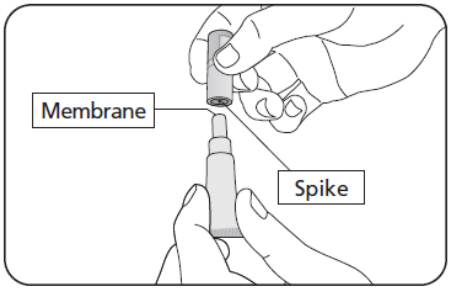


1. Pull off the cap

- 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.

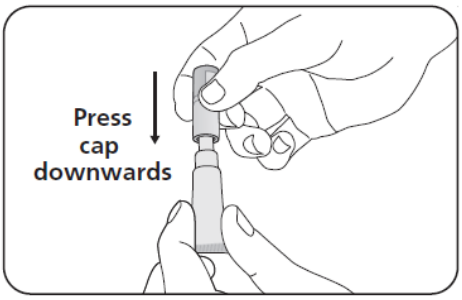


3. Position the cap to open the tube

- 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.



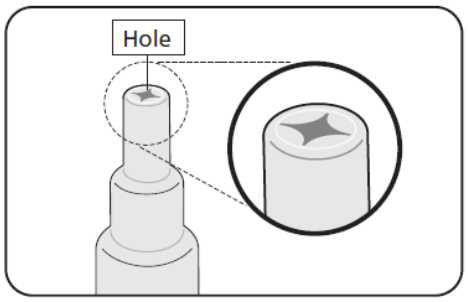
C Check the tube has opened correctly

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

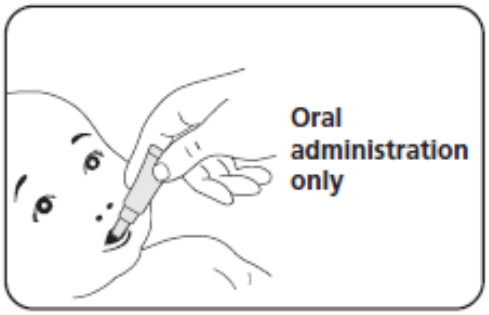
- If the membrane has not been pierced return to section B and repeat steps 2, 3 and 4.



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

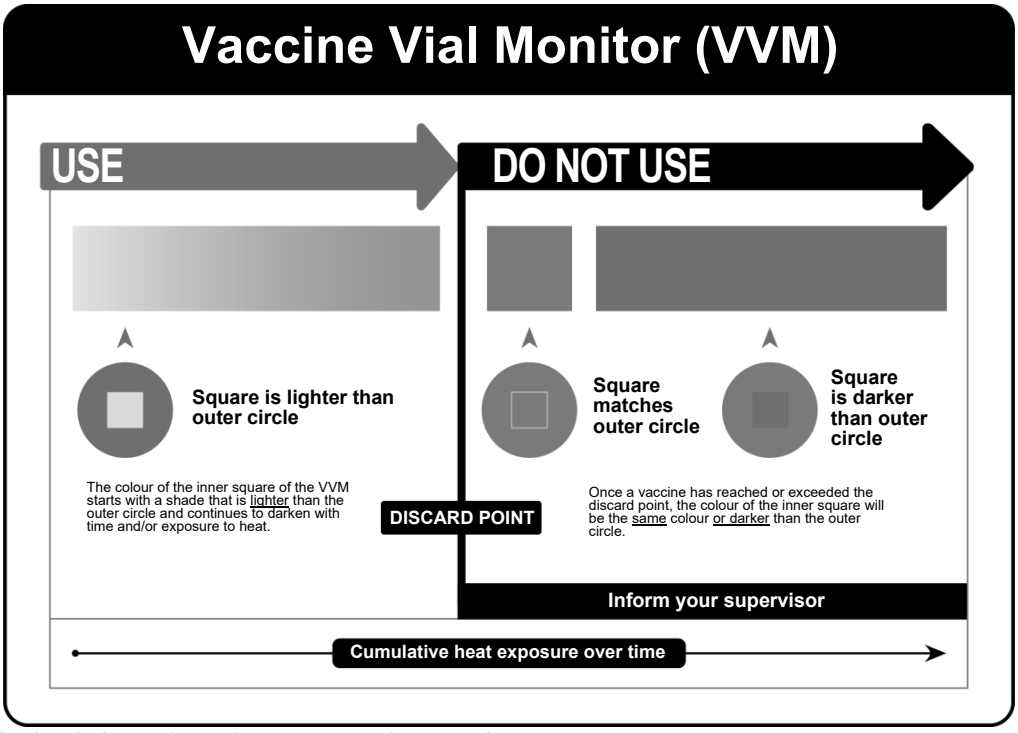
- Squeeze the liquid gently into the side of the child's mouth - towards the inside of their cheek.
- You may need to squeeze the tube a few times to get all of the vaccine out - it is okay if a drop remains in the tip of the tube.

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

Vaccine Vial Monitor (see VVM infographic at the end of the leaflet)
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 inner square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the outer circle, then the vaccine can be used. As soon as the colour of the inner square is the same colour as the outer circle or of a darker colour than the outer circle, 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.



For further information, please contact the manufacturer.

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