



#### **4.4 Special warnings and special precautions for use**

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**<sup>TM</sup> should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, however, is not a contra-indication for immunisation.

The administration of **Rotarix**<sup>TM</sup> should be postponed in subjects suffering from diarrhoea or vomiting.

**Rotarix**<sup>TM</sup> has not specifically been studied in subjects with known primary and secondary immunodeficiencies including HIV positive infants.

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 section 5.1).

**Rotarix**<sup>TM</sup> does not protect against gastro-enteritis due to other pathogens than rotavirus.

**ROTARIX**<sup>TM</sup> SHOULD UNDER NO CIRCUMSTANCES BE INJECTED.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Co-administration studies involving more than 5000 subjects have demonstrated that **Rotarix**<sup>TM</sup> can be given concomitantly with any of the following administered either as monovalent or as combination vaccines: 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 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 2000 subjects, were performed where **Rotarix**<sup>TM</sup> and OPV were administered two weeks apart. The immune response to **Rotarix**<sup>TM</sup> and OPV was unaffected. In an immunogenicity study, involving approximately 150 subjects, **Rotarix**<sup>TM</sup> was concomitantly administered with OPV. The immune response to OPV, as well as the response to **Rotarix**<sup>TM</sup> after the second dose, were unaffected. **Rotarix**<sup>TM</sup> 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**<sup>TM</sup> should be respected.

#### **4.6 Pregnancy and lactation**

**Rotarix**<sup>TM</sup> 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.

#### **4.7 Effects on ability to drive and use machines**

Not applicable.

#### **4.8 Undesirable effects**

Clinical trials

The occurrence of undesirable effects was actively monitored up to 14 days after vaccination in 9 placebo controlled clinical trials involving the administration of more than 72,930 doses of **Rotarix**<sup>TM</sup> to 37,216 infants in the first six months of life. The adverse reaction profile observed in the subjects receiving **Rotarix**<sup>TM</sup> was similar to the adverse reaction profile observed in subjects receiving placebo. No increase in the incidence or severity of these

reactions was seen with the second dose.

Adverse events considered by the investigator as being at least possibly related to **Rotarix**<sup>TM</sup> vaccination have been categorised by frequency as:

Very common:	≥ 10%
Common:	≥ 1% and < 10%
Uncommon:	≥ 0.1% and < 1%
Rare:	≥ 0.01% and < 0.1%
Very rare:	< 0.01%

- In the two clinical trials where **Rotarix**<sup>TM</sup> was administered alone, a total of 703 doses of **Rotarix**<sup>TM</sup> were administered to 366 subjects.

The following are the observed adverse reactions:

Psychiatric disorders:

*Very common:* irritability

*Uncommon:* crying, sleep disorder

Nervous system disorders

*Uncommon:* somnolence

Gastrointestinal disorders:

*Very common:* loss of appetite

*Common:* diarrhoea, vomiting, flatulence, abdominal pain, regurgitation of food

*Uncommon:* constipation

General disorders and administration site conditions

*Common:* fever, fatigue

- In six clinical trials, **Rotarix**<sup>TM</sup> was co-administered with other paediatric vaccines (see section 4.5). More than 10,300 doses of **Rotarix**<sup>TM</sup> were administered to 5,177 subjects.

The following additional adverse reactions have been categorised by frequency:

Infections and infestations

*Rare:* upper respiratory tract infection

Respiratory, thoracic and mediastinal disorders

*Rare:* hoarseness, rhinorrhoea

Gastrointestinal disorders:

*Very rare:* gastro-enteritis

Skin and subcutaneous tissue disorders

*Rare:* dermatitis, rash

Musculoskeletal and connective tissue disorders

*Rare:* muscle cramp

- In a large safety trial where 63,225 subjects were vaccinated either with **Rotarix**<sup>TM</sup> or with placebo. The observed point estimate for the Risk Difference of definite intussusception (-0.32/10.000) gave evidence of no increased risk of intussusception in

the **Rotarix**<sup>TM</sup> group as compared with the placebo group.

#### **4.9 Overdose**

Not applicable.

### **5 - Pharmacological Properties**

Pharmaco-therapeutic group: viral vaccines, ATC code: JO7BH

#### **5.1 Pharmacodynamic properties**

Clinical studies, conducted in Europe, North America, Latin America and Asia, have demonstrated that **Rotarix**<sup>TM</sup> is a safe and well tolerated vaccine.

Protective efficacy of **Rotarix**<sup>TM</sup> against any and severe rotavirus gastro-enteritis and against hospitalisation for gastro-enteritis has been evaluated. Severe gastro-enteritis was defined as 11 or more points on the established and widely used Vesikari 20-point scale (Scand J Infect Dis 1990;22:259-267) 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.

Clinical studies, which involved approximately 1,600 subjects, have been conducted in Latin America and Europe. During the first year of life, the observed vaccine efficacy against severe rotavirus gastro-enteritis after two doses of **Rotarix**<sup>TM</sup> ranged from 78.3 to 90.0%. The observed vaccine efficacy against any rotavirus gastro-enteritis ranged between 62.9 and 73.0%. Protective efficacy against hospitalisation for rotavirus gastro-enteritis was 86.0%.

Protective efficacy of **Rotarix**<sup>TM</sup> during the second year of life has been evaluated in approximately 250 subjects in Europe. The observed vaccine efficacy against severe rotavirus gastro-enteritis after two doses of **Rotarix**<sup>TM</sup> was 83.4% and against any rotavirus gastro-enteritis 72.8%.

In clinical trial settings where non-G1 serotypes, such as G2, G3, G4 and G9 (which has been frequently observed in recent outbreaks), were circulating, cross-protection has been evaluated. The vaccine efficacy against severe gastro-enteritis caused by non-G1 serotypes was 74.0%.

**Rotarix**<sup>TM</sup> does not protect against non-rotaviral gastro-enteritis, or against diarrhoea due to other infectious and non-infectious causes.

#### **5.2 Pharmacokinetic properties**

Evaluation of pharmacokinetic properties is not required for vaccines.

#### **5.3 Preclinical safety data**

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

### **6 - Pharmaceutical Particulars**

#### **6.1 List of excipients**

Lyophilised vaccine:

Sucrose

Dextran

Sorbitol  
Amino acids  
Dubelcco's Modified Eagle Medium (DMEM)

Liquid diluent:

Calcium carbonate  
Xanthan  
Water for injections q.s. ad

**6.2 Incompatibilities**

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

**6.3 Shelf-life**

The expiry date of the vaccine is indicated on the label and packaging.

**6.4 Special precautions for storage**

Before reconstitution:

The lyophilised vaccine must be stored at +2°C/+8°C (in a refrigerator).

The liquid diluent may be stored at either +2°C/+8°C or at ambient temperature (the storage temperature must not exceed 37°C).

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

Do not freeze.

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

After reconstitution:

After reconstitution, the vaccine should be administered promptly or kept in the refrigerator (+2°C/ +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/+25°C). However, these data are not recommendations for storage.

**6.5 Nature and contents of container**

Lyophilised vaccine in glass vial (Type I, Ph. Eur.) with stopper (butyl rubber).

Liquid diluent (1 ml) in glass prefilled syringe (Type I, Ph. Eur.) with a plunger stopper (butyl rubber).

Pack size of 1, 10, 25, 50 and 100.

Transfer device for reconstitution.

**6.6 Instructions for use and handling**

A white deposit and clear supernatant is observed upon storage of the syringe containing the liquid diluent. 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 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 lyophilised vaccine
2. Connect the transfer device onto the vial by pushing it downwards until the transfer device is properly and solidly placed
3. Shake the syringe containing the liquid diluent vigorously. The shaking 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 device by pushing it
6. Inject the entire contents of the syringe into the vial containing the lyophilised vaccine
7. Shake the vial and examine for complete dispersal. 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 device
10. Administer the entire content of the syringe **ORALLY** (on the inside of the cheek). The child should be seated in a reclining position. If the vaccine is not administered immediately, the syringe containing the reconstituted vaccine should be shaken again before **ORAL** administration. **Do not inject.**