Unit: Technical Assessment Unit

Public assessment report for biological products

Rotarix Vaccine

Administrative information:

Trade name of the medicinal product:	Rotarix Vaccine
INN (or common name) of the active substance(s):	Live attenuated human rotavirus
Manufacturer of the finished product	GlaxoSmithKline Biologicals S.A
Marketing Authorization holder	GlaxoSmithKline Biologicals S.A
Applied Indication(s):	Active immunization of infants against gastro-enteritis due to Rotavirus.
Pharmaceutical form(s) and strength(s):	1.5 ml containing not less than $10^{6.0}$ $CCID_{50}$ of live attenuated Rotavirus.
Route of administration	Oral
Type of registration (EMA/FDA – Local)	EMA

List of abbreviations

HRV	Live attenuated human rotavirus
GSK	GlaxoSmithKline Biologicals
MA	Marketing authorization
WHO	World Health Organization
Ph. Eur	European Pharmacopoeia
UNICEF	United Nations Children's Fund
VP	viral proteins
RNA	Ribonucleic acid
MS	Master seed
WS	Working seed
INN	International Nonproprietary Name
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use.
PAHO	Pan American Health Organization
CCID50	cell culture infectious dose 50%
DMEM	Dulbeccoís Modified Eagle Medium
OPV	Oral Polio Vaccine
GMP	Good Manufacturing Practices
CI	Confidence Interval

GMCs	Geometric Mean Concentrations
IS	intussusception
RV GE	rotavirus gastroenteritis

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1. **General introduction about the product including brief description of the AI, its mode of action and indications:**

- The active ingredient of GlaxoSmithKline (GSK) Biologicals Human Rotavirus (HRV) vaccine (Rotarix) is a live attenuated strain of human rotavirus (HRV), which belongs to the G1 serotype and the [P8] genotype.

The liquid vaccine is presented in glass prefilled syringe (type I, Ph. Eur) with a plunger stopper (butyl rubber) or in polyethylene tubes provided with a nozzle finished by an opening, sealed by an extractable strip and protected by a cap in polypropylene.

The HRV vaccine must be given by the oral route. The vaccination course consists of two doses with an interval of at least 4 weeks between doses.

Quality aspects:

1.2.1 Introduction

As mentioned in the aforementioned section.

Manufacture, process controls and characterization:

Manufacturer:

Manufacturing of the drug substance (active ingredient):
GlaxoSmithKline Biologicals S.A
Parc de la Noire Epine
Rue de Flemming, 20
1300 Wavre
Belgium

Description of Manufacturing Process and Process Controls.

The HRV live attenuated vaccine is produced on Vero cells, derived from Vero cell strain. Production is based on the seed lot principle. The seed lots are produced on the Vero cell substrate and the working seed (WS) is derived from the master seed (MS) lot by one additional passage.

Control of Materials.

The quality control tests performed at various stages of the preparation of the vaccine bulks are provided in MA file.

- **Controls of Critical Steps and Intermediates.**

The tests and acceptance criteria for the control of critical steps in the manufacturing process of HRV purified bulks are presented in MA file.

- **Specification**
  - Specifications applied to the HRV bulks are based on ICH and Ph. Eur. Requirements relevant for live attenuated vaccines.
  - **Reference Standards or Materials.**
  - Company uses internal control for the potency test with an established titer.

- **Container closure system**
  The harvests and purified bulks are stored in polyethylene containers as used for the other bulk vaccines manufactured by the Company.
- **Stability of drug substance**

Recommended storage condition: -45°C.
The proposed shelf-life is 24 months for the harvest and 72 months for the purified bulk.

2.2.3 Drug product:

Manufacture of the drug product:

- Description of manufacturing process and process controls along with manufacturers and responsibilities

Manufacturer:

The manufacture and the final packaging of HRV liquid vaccine is performed by:
GlaxoSmithKline Biologicals SA
Rue de l'Institut 89
1330 Rixensart
Belgium
Or by:
GlaxoSmithKline Biologicals SA
Parc de la Noire Epine
Rue Flemming, 20
1300 Wavre
Belgium

- **Product specification:**

- All the other excipients are described in Ph. Eur.
- Analytical procedures for excipients are described in Ph. Eur, and in-house SOPs and performed accordingly.
  - **Reference Standards or Materials.**
  - Reference material (internal control) for the potency test is Rotarix lot of HRV lyophilized vaccine with an established titer.
  - **Container closure system.**
    The HRV liquid vaccine is filled in:
    • 1.75 ml clean, sterile syringe, uncolored glass (Type I, Ph. Eur.) fitted with rubber tip caps. Plunger stoppers are of grey butyl rubber.
    • 3 ml sterile polyethylene tubes provided with a nozzle finished by an opening, sealed by an extractable strip and protected by a cap in polypropylene.
    Stability of the drug product.

-Based on available stability data,
approved Shelf Life: 36 months
approved Storage Conditions: 2-8 °.
-Accelerated stability study for 7 days at 37°C and Arrhenius study

2. Non–clinical aspect:

The data from the preclinical studies presented in the original dossier for the licensed lyophilised vaccine, Rotarix™ are applicable for the HRV liquid formulation. This is based on the following:

• The low relevance of animal models for the evaluation of immunogenicity induced by human rotavirus vaccine,
• The same active ingredient is used for both formulations,
• No novel excipient of toxicological concern is involved in the liquid formulation,

Therefore, no additional preclinical studies were required to support the formulation change of the HRV vaccine.

3. Clinical aspect:

GlaxoSmithKline (GSK) developed **a live attenuated rotavirus oral vaccine containing the (RIX4414 strain)** of human rotavirus formulated as a liquid preparation. The clinical program comprised 4 studies:

- Phase II: 2 studies
- Phase III: 2 studies

These studies consistently evaluated the safety, efficacy, and immunogenicity of the vaccine "liquid formulation" in healthy infants "rotavirus-naïve infants aged approximately two months" previously uninfected with the already licensed lyophilized formulation (HRV).

➢ **<u>Clinical Efficacy and Immunogenicity</u>**

- **Comparable Immunogenicity:**
  Across all studies, the **liquid formulation demonstrated immunogenicity equivalent** to that of the lyophilized vaccine, based on **IgA seroconversion rates, geometric mean concentrations (GMCs), and vaccine take**.
- **Dosing Schedule Findings (Study Rota-051):**
  The **0,1-month schedule** showed **lower seroconversion rates and GMCs** than the **0, 2-month schedule**, likely due to **immature immune response** and **maternal antibody interference** in younger infants.
  Nevertheless, delaying vaccination must be balanced against the **risk of early natural rotavirus infection**, as evidenced by seroconversion among placebo recipients at 13-17 weeks of age.
- **Equivalence Between Formulations:**
  Studies **Rota-057, Rota-048, and Rota-061** confirmed **no significant differences** in immunogenicity, reactogenicity, or safety between the **lyophilized and liquid formulations**. Similarly, **no difference in rotavirus gastroenteritis (RV GE) incidence** was observed between the two formulations.
- **Lot-to-Lot Consistency:**
  Three consecutive production lots of the liquid formulation met predefined criteria for **GMC ratios within the 0.5–2.0 interval**, confirming **manufacturing consistency**.

- **Non-Inferiority Demonstrated:**
  - **Seroconversion rates:** Upper limit of 95% CI <10% (predefined margin).
  - **IgA antibody levels:** GMC ratio upper limit <2 (predefined margin).
    These confirm **non-inferiority** of the liquid versus lyophilized vaccine.

➢ **Clinical Safety**

- The **safety profile** of the liquid formulation was **comparable to the licensed formulation**, based on **data from 1,933 vaccinated infants**.
- Although this sample size is not large enough to exclude a small increase in **intussusception (IS)** risk, the CHMP agreed that, since both formulations contain the **same strain, potency, and dosing schedule**, the **risk of IS is expected to be similar**.
  post-marketing surveillance was deemed appropriate for continued IS monitoring.
- **Unsolicited grade 3 symptoms** were slightly more frequent with the liquid formulation (6.3% vs 3%), but without clinical significance; solicited adverse events were comparable between formulations.

➢ **Benefit–Risk Evaluation**

GSK developed the **liquid Rotarix** to improve **handling, storage, and supply logistics** without altering the vaccine's composition or immunological properties.
The collective clinical data demonstrate that:

- The **immune response**, **reactogenicity**, and **safety profile** of the liquid formulation are **comparable** to the licensed lyophilized product.
- **Lot-to-lot consistency** and **non-inferiority** were clearly established.
- **No new safety signals** or differences in clinical outcomes were identified.

From a regulatory perspective, the **benefit–risk balance** strongly favors the liquid formulation, which offers several **practical and logistical advantages**:

1. Simplified preparation and administration.
2. Improved supply chain and cold-chain efficiency.
3. Reduced packaging size and environmental impact.
4. Increased manufacturing capacity to meet global demand.

➢ **Overall Conclusion**

The totality of evidence supports that the **liquid Rotarix formulation** maintains **equivalent efficacy, immunogenicity, and safety** compared with the currently approved lyophilized formulation.

General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.

https://www.ema.europa.eu/en/documents/overview/rotarix-epar-summary-public_en.pdf