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EMA/170635/2015
Committee for Medicinal Products for Human Use (CHMP)

# CHMP assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No1901/2006, as amended

Rotarix

rotavirus vaccine, live

Procedure No: EMEA/H/C/000639

P46 063

**Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted**

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# I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed.

# 1. RECOMMENDATION

The Rapporteur endorses the conclusions drawn by the MAH and does not require any further action to be taken.

# 2. INTRODUCTION

On 26/01/2011, the MAH submitted 2 completed paediatric study(ies) for Rotarix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study(ies) do not influence the benefit risk for Rotarix and that there is no consequential regulatory action.

# 3. SCIENTIFIC DISCUSSION

**Information on the pharmaceutical formulation used in the study(ies)**

This assessment report concerns two paediatric studies, respectively a post marketing surveillance and a Phase I study to monitor the reactogenicity and safety of the Rotarix vaccine.

Rotarix is indicated for the active immunisation of infants from the age of 6 weeks for prevention of gastroenteritis due to rotavirus infection, and has been shown to be effective against G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8] rotavirus types.

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.

**Clinical aspects**

**1. Introduction**

The MAH submitted final report(s) for:

- 112896 (Rota-071 PMS): Post marketing surveillance to monitor the reactogenicity and safety of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus vaccine, Rotarix™ when administered according to the Prescribing Information to Indian infants.
- 113552 (Rota-073): Phase I, double-blind, randomised, placebo controlled study to evaluate the reactogenicity and safety of a single oral dose of GlaxoSmithKline (GSK) Biologicals' live ttenuated liquid human rotavirus (HRV) vaccine in healthy children aged 2 to 6 years in China.

**2. Clinical study(ies)**

**<u>112896 (Rota-071 PMS): Post marketing surveillance to monitor the reactogenicity and safety of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus vaccine, Rotarix™ when administered according to the Prescribing Information to Indian infants.</u>**

- **Methods**

  - Objective(s)

    *<u>Primary:</u>*

- To assess the reactogenicity of *Rotarix* in terms of occurrence of at least one Grade "2" or Grade "3" fever, vomiting or diarrhoea within the 8-day (Day 0–Day 7) follow-up period after any *Rotarix* vaccination.

*Secondary:*

- To assess the reactogenicity of *Rotarix* in terms of occurrence of solicited adverse events (AEs) within a 8-day (Day 0-Day 7) follow-up period after each dose of the vaccination.
- To assess the safety of *Rotarix* in terms of occurrence of unsolicited AEs within a 31-day (Day 0- Day 30) follow-up period after any vaccination, according to Medical Dictionary for Regulatory Activities (MedDRA) classification.
- To assess the safety of *Rotarix* in terms of serious adverse events (SAEs) throughout the surveillance period after the first dose was administered in the Post Marketing Surveillance (PMS).

- Study design

This PMS was an open, self-contained, single group PMS. Subjects who were prescribed Rotarix in the course of their normal clinical practice were enrolled in this study. Two doses of Rotarix were administered as per the Prescribing Information (PI). First vaccination was administered from the age of 6 weeks and the second vaccination was administered at least 4 weeks after the first dose. Dose 2 was given before 24 weeks of age. Subjects who had received one dose of Rotarix prior to start of the PMS were also enrolled. All subjects were allowed to receive routine vaccinations concurrently with Rotarix according to the Expanded Programme on Immunisation (EPI). No blood samples were collected in this PMS. Data collection was done by Remote Data Entry (RDE) using electronic Case Report Forms (eCRFs).

- Study population /Sample size

**II.** The number of subjects to be included in the PMS was determined to be 371 subjects to reach 500 evaluable doses. Considering a 10% dropout rate, there were 334 evaluable subjects in this PMS.

**III.** Assuming that 50% of the enrolled subjects would receive 2 doses (Dose 1 and Dose 2) of *Rotarix* in this PMS, at least 500 evaluable doses of *Rotarix* would be obtained.

- Treatments

Subjects received two oral doses of *Rotarix* according to a 0, 1 month schedule. The duration of the PMS, per subject, was approximately 2-3 months. For the subjects who had received one dose of *Rotarix* prior to the start of the PMS and for subjects who received Dose 2 of *Rotarix* at another clinic not participating in this surveillance, the duration was approximately 1 month.

Each 1 millilitre (mL) dose of vaccine contained not less than $10^{6.0}$ median Cell Culture Infective Dose ($CCID_{50}$) of RIX4414 Live Attenuated HRV strain lyophilised with active substance. As this was a PMS study, commercial lots of the vaccine that were purchased locally by the subject's parents/guardians were used. Hence, lot numbers for the vaccine are not known.

- Outcomes/endpoints

**IV.** *Primary endpoint*:

- Occurrence of at least one Grade "2" or Grade "3" fever, vomiting or diarrhoea during the 8-day (Day 0–Day 7) follow-up period after any *Rotarix* vaccination.

**V.** *Secondary endpoints:*

- For each type of solicited symptom, occurrence of the symptom within the 8-day (Day 0-Day 7) follow-up period after each dose of the vaccination.
- Occurrence of unsolicited symptoms during the 31-day (Day 0-Day 30) follow-up period after any vaccination, according to MedDRA classification.

- Occurrence of SAEs throughout the surveillance period following the first dose administered in the PMS.

- Statistical Methods

**VI.** The analyses were performed according to the protocol and as described in the study reporting and analysis plan (RAP). Analysis was performed on the TVC.

**VII.** *Analysis of demography*

**VIII.** The mean, range and standard deviation (SD) of height in (centimetres [cm]) and weight (in kilograms [kg]) at each dose of Rotarix vaccination was calculated. The mean, range and SD of age in weeks at each vaccination were calculated. The racial and gender composition had also been presented. The distribution of subjects enrolled among the PMS centres was tabulated.

**IX.** *Analysis of reactogenicity and safety*

**X.** The overall incidence, with exact 95% confidence interval (CI), of any AEs (solicited or unsolicited) during the 8-days solicited follow-up period was tabulated, for each dose, for overall per dose and overall per subject. The same calculations were done for any AEs (solicited or unsolicited); rated as Grade "3" and for those assessed as causally related to vaccination.

**XI.** Percentage of doses and of subjects reporting fever, vomiting or diarrhoea graded "2" or "3" in intensity during the solicited follow-up period was calculated. The incidence, with exact 95% CI, of each individual solicited AE, was calculated, over the solicited follow-up period, after each dose, for overall per dose and overall per subject.

**XII.** The same calculations were done for each individual solicited AE rated as Grade "3" and for each individual solicited AE assessed as causally related to vaccination. The verbatim reports of unsolicited AEs were reviewed by a physician and the signs and symptoms were coded according to MedDRA. Every verbatim term was matched with the appropriate preferred term (PT).

**XIII.** The percentage of subjects with unsolicited AEs occurring within the 31-days follow-up period after any dose with its exact 95% CI was tabulated by PT. Similar tabulations were done for unsolicited AEs rated as Grade "3" and for those with causal relationship to vaccination. The percentage of subjects who received at least one concomitant medication during the 8-day (Day 0-Day 7) solicited follow-up period was tabulated by type of medication, with exact 95% CI. Similar tabulations were done for subjects who received concomitant medication during the entire PMS period. SAEs reported during the PMS period were to be described in detail.

➢ **Results**

- Recruitment/ Number analysed

A total of 332 subjects were enrolled of which 272 completed the PMS. None of the withdrawals was considered causally related to the vaccine. The mean age of the subjects in the TVC at Dose 1 was 10.4 weeks (range: 5 weeks to 23 weeks) and at Dose 2 was 15.6 weeks (range: 10 weeks to 29 weeks). The subjects were predominantly of "Asian - Central/South Asian heritage (58.1%); 53.3% of the subjects were male and 46.7 % of the subjects were female.

**Table 1: Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Total vaccinated cohort)**

| | HRV group |
|---|---|
| Number of subjects vaccinated | 332 |
| Number of subjects completed | 272 |
| Number of subjects withdrawn | 60 |
| **Reasons for withdrawal:** | |
| Serious Adverse Event | 0 |
| Non-serious adverse event | 2 |
| Protocol violation | 1 |
| Consent withdrawal (not due to an adverse event) | 4 |
| Migrated/moved from study area | 4 |
| Lost to follow-up (subjects with incomplete vaccination course) | 33 |
| Lost to follow-up (subjects with complete vaccination course) | 0 |
| Others* | 16 |

HRV= Human rotavirus vaccine
Vaccinated= number of subjects who were vaccinated in the study
Completed= number of subjects who completed last study visit
Withdrawn= number of subjects who did not come for the last visit
*Reasons for Others are described in text.

Most of the subjects (21.5% and 18.4%) received diphtheria, tetanus, pertussis, hepatitis B, inactivated poliovirus and *Haemophilus influenzae* type b (DTPa+IPV+Hib) vaccine along with Dose 1 and Dose 2 of *Rotarix* vaccine, respectively. 17.0% also received *Haemophilus influenzae* type b (Hib) vaccine between Dose 1 and Dose 2.

- Safety results

The percentage of subjects reporting any AE (solicited or unsolicited) during the 8-day (Day 0-Day 7) follow-up period was 39.5%.

The percentage of subjects reporting any AEs (solicited or unsolicited) rated as Grade "3" in intensity during the 8-day (Day 0-Day 7) follow-up period was 9.0% and those assessed as causally related to vaccination was 8.1%.

*Primary endpoint:*

- The percentage of subjects reporting Grade "2" or Grade "3" solicited AEs (fever, vomiting, and diarrhoea) during the 8-day (Day 0-Day 7) follow-up period was 12.7%.

*Secondary endpoints:*

*Solicited general AEs:*

- Irritability was the most frequently reported solicited AE after each dose; reported for 23.0% and 13.2% of subjects following Dose 1 and Dose 2, respectively.
- The most frequently reported Grade "3" solicited AE was vomiting in 4.5% of the subjects following Dose 1 and Irritability in 1.1% of the subjects following Dose 2.
- The most frequently reported solicited AE with a causal relationship to vaccination was vomiting, in 3.0% of the subjects following Dose 1.and fever in1.8% of the subjects following Dose 2.

*Unsolicited AEs:*

- The percentage of subjects reporting at least one unsolicited AE during the 31-day (Day 0-Day 30) follow-up period was 6.9%.
- Grade "3" unsolicited AEs (nasopharyngitis and rhinorrhoea) were reported for 1 subject during the 31-day (Day 0–Day 30) follow-up period.
- Unsolicited AEs with causal relationship to vaccination were reported for 0.6% of subjects during the 31-day (Day 0–Day 30) follow-up period.

*Serious adverse events:*

- No SAEs were reported in this study.

*Withdrawals due to adverse events /serious adverse events:*

- Two subjects were withdrawn from the study due to non serious AE (diarrhoea). The AEs were not considered to be causally related to vaccination by the investigator.

**113552 (Rota-073): Phase I, double-blind, randomised, placebo controlled study to evaluate the reactogenicity and safety of a single oral dose of GlaxoSmithKline (GSK) Biologicals' live ttenuated liquid human rotavirus (HRV) vaccine in healthy children aged 2 to 6 years in China.**

➢ **Methods**

- Objective(s)

*Primary:*

- To assess the reactogenicity of a single oral dose of GSK Biologicals' liquid HRV vaccine when compared to placebo group, in terms of solicited adverse events (AEs) in healthy children aged 2 to 6 years.

*Secondary:*

- To assess the safety of a single oral dose of GSK Biologicals' liquid HRV vaccine when compared to placebo group, in terms of unsolicited AEs and serious adverse events (SAEs) in healthy children aged 2 to 6 years.

- Study design

Phase I, double-blind, randomised (1:1), placebo-controlled study with two parallel groups:

- HRV vaccine group (henceforth referred to as HRV group): subjects received a single dose of the liquid HRV vaccine at Day 0 (N=25).
- Placebo group: subjects received a single dose of the placebo at Day 0 (N=25).

All subjects were allowed to receive routine childhood vaccinations according to the local immunization practice, including diphtheria and tetanus toxoids vaccine [DT], diphtheria, tetanus and acellular pertussis vaccine [DTPa], diphtheria, tetanus and whole-cell pertussis vaccine [DTPw], hepatitis A vaccine [HepA], Japanese encephalitis vaccine [JapEnc], meningococcal serogroup A vaccine [MenA], meningococcal serogroup A and serogroup C vaccine [MenAC], measles and mumps vaccine [MM], measles, Mumps and rubella vaccine [MMR] and oral poliovirus vaccine [OPV]). No blood samples were collected in this study.

- Study population /Sample size

**XIV.** Healthy male and female subjects of Chinese ethnicity aged between, and including 2 and 6 years at the time of vaccination. Written informed consent was obtained from the parents or Legally Acceptable Representatives (LARs) of each subject.

**XV.**

| Number of subjects: | Total | HRV group | Placebo group |
|---|---|---|---|
| Planned, Enrolled and Completed | 50 | 25 | 25 |
| Total vaccinated cohort (TVC) | 50 | 25 | 25 |
| According-to-Protocol (ATP) cohort for safety and reactogenicity | 50 | 25 | 25 |

- Treatments

Subjects in the HRV group received a single oral dose of the liquid HRV vaccine. Each 1.5 mL dose of GSK Biologicals' liquid HRV vaccine contained at least $10^{6.0}$ median Cell Culture Infective Dose ($CCID_{50}$) of RIX4414 HRV strain, 2.26 mg of Dulbecco's Modified Eagle Medium (DMEM), 132.74 mg of Di-sodium Adipate and 55% of sucrose (w/w).

Subjects in the placebo group received a single oral dose of the placebo. Each 1.5 mL dose of GSK Biologicals' placebo for liquid HRV vaccine contained 2.26 mg of DMEM, 132.74 mg of Di-sodium Adipate and 55% of sucrose (w/w).

- Outcomes/endpoints

*Primary endpoint*

- Occurrence of each solicited AE within the 8-day (Day 0-Day 7) follow-up period after the liquid HRV vaccine/placebo dose.

*Secondary endpoints*

- Occurrence of unsolicited AEs within 31-day (Day 0-Day 30) follow-up period after the liquid HRV vaccine/placebo dose according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of SAEs throughout the study period following the HRV vaccine/placebo dose.

- Statistical Methods

**XVI.** *Analysis of demographics/baseline characteristics*

**XVII.** The mean, range and standard deviation (SD) of age in years, height in cm, weight in kg at Visit 1 were calculated per group and overall. The racial and gender composition per group were presented.

**XVIII.** *Analysis of safety*

**XIX.** Analyses were performed on the TVC. The overall incidence, with exact 95% confidence interval (CI), of any solicited AEs during the 8-day (Day 0-Day 7) follow-up period after vaccination was tabulated. The same calculations were done for any solicited AEs rated as grade "3" and for those assessed as causally related to vaccination. The overall incidence, with exact 95% CI, of any AEs (solicited or unsolicited) during the 8-day (Day 0-Day 7) solicited follow-up period after vaccination was tabulated. The same calculations were done for any AEs (solicited or unsolicited) rated as grade "3" and for those assessed as causally related to vaccination. Note: Intensity of fever was assessed by considering the grading scales recommended by the Chinese authorities as well as GSK Biologicals. Analysis for each intensity grading scale was performed separately.

**XX.** The incidence, with exact 95% CI, of each individual solicited AEs, was calculated, over the follow-up period after vaccination. The same calculations were done for each individual solicited AEs rated as grade "3" and those assessed as causally related to vaccination. The verbatim reports of unsolicited AEs were reviewed by a physician and the signs and symptoms were coded according to MedDRA. Every verbatim term was matched with the appropriate Preferred Term (PT). The percentage of subjects with unsolicited AEs occurring within 31-day (Day 0-Day 30) follow-up period after vaccination with its exact 95% CI was tabulated by System Organ Class (SOC) and PT. Similar tabulation was done for unsolicited AEs rated as grade "3" and for those with causal relationship to vaccination.

**XXI.** The percentage of subjects who received at least one concomitant medication during the 8-day (Day 0-Day 7) solicited follow-up period after vaccination was tabulated by type of medication, with exact 95% CI. Similar tabulations were done for subjects who receive concomitant medication during the study period.

**XXII.** SAEs reported during study period were to be described in detail.

- **Results**

  - Recruitment/ Number analysed

    The mean age of the subjects in the TVC was 3.8 years (range: 2 years to 5 years) at the time of vaccination. All subjects were of Chinese origin and 50.0% of the subjects were male and 50.0% were female. The mean height of the subjects was 101.3 cm (range: 89.0 cm to 114.0 cm) and mean weight of the subjects was 16.4 kg (range: 13.0 kg to 22.0 kg)

  - Safety results

    At least one AE (solicited and unsolicited) was reported for 56.0% of the subjects in the HRV group and for 52.0% of the subjects in the placebo group during the 8-day (Day 0-Day 7) solicited follow-up period after vaccination.

    The percentage of subjects with the report of at least one solicited AE was 52.0% in each group during the 8-day (Day 0-Day 7) follow-up period after vaccination.

    8.0% of the subjects in the HRV group and for 4.0% of the subjects in placebo group reported at least one AE (solicited and unsolicited) with causal relationship to vaccination, as assessed by the investigator.

Cough was the most frequently reported solicited general AE during the 8-day (Day 0-Day 7) follow-up period after vaccination. It was reported for 40.0% of the subjects in the HRV group and for 48.0% of the subjects in the placebo group.

Grade 3 diarrhoea was reported for 1 subject (4.0%) in the placebo group. None of the subjects in the HRV group were reported for any Grade 3 AEs during the 8-day (Day 0-Day 7) follow-up period after vaccination.

Diarrhoea was reported for one subject (4.0%) in the HRV group, which was considered causally related to the vaccination by the investigator. In the Placebo group, cough was reported for one subject (4.0%) and fever was reported for one subject (4.0%) which were both considered causally related to the vaccination by the investigator during the 8-day (Day 0-Day 7) follow-up period after vaccination.

*Unsolicited AEs*

The percentage of subjects with the report of at least one unsolicited AE classified by MedDRA SOC was 44.0% [95% CI: 24.4%; 65.1%] in the HRV group and 52.0% [95% CI: 31.3%; 72.2%] in the placebo group during the 31-day (Day 0-Day 30) post vaccination period.

*SAEs*

None of the subjects experienced any SAEs and there were no fatal cases reported in the study.

*Withdrawals due to (S)AEs*

None of the subjects were withdrawn due to an AE or an SAE during the course of the study.

*Concomitant medication/ vaccination*

The percentage of the subjects who were given any concomitant medication during the 8-day (Day 0-Day 7) follow-up period after vaccination was 28% in the HRV group and 20% in the placebo group.

**3. Discussion on clinical aspects**

*Study 112896 (Rota-071 PMS)*

This PMS study was conducted in India to evaluate the reactogenicity and safety of two oral doses of *Rotarix* when given to healthy infants aged between 6 to 24 weeks.

Results showed that, vomiting was the most frequently reported Grade "3" solicited AE in this study, similar to that observed in the clinical trial conducted in India. Incidences of at least one Grade "2" or Grade "3" fever, vomiting or diarrhoea within the 8-day follow-up period lay at 12.7% of the subjects and the incidence of at least one unsolicited symptom within 31-day follow-up period was seen in 6.9%. These results were similar to those observed in another PMS conducted in the same geographic region.

Peak incidences for diarrhoea, fever and vomiting during the 8-day (Day 0-Day 7) follow-up after any doses were absent. Furthermore, no IS cases,fatalities or ,other SAEs were reported.

Overall, the two-dose vaccination course of *Rotarix* was well tolerated in healthy Indian infants. The safety and reactogenicity data of *Rotarix* reported in this study was in line with the existing safety profile of the vaccine.

*Study 113552 (Rota-073)*

Adhering to the requirements of Chinese regulatory authorities and in order to support the licensure of the GSK Biologicals' liquid HRV vaccine in China, it was necessary to conduct a Phase I safety study in older children prior to conducting a study in the targeted infant population.

Thus, this study was conducted to collect reactogenicity and safety data of a single dose of liquid HRV vaccine in children aged 2-6 years.

In this study, the reactogenicity and safety profile of the liquid HRV vaccine showed to be similar to that of the placebo in terms of solicited AEs and unsolicited AEs, with the liquid HRV vaccine being well tolerated in the age group of 2-6 years and no reports of any SAEs or fatal cases. The results of this study will support in the conduct of further clinical studies with the liquid HRV vaccine in the infant population in China.

## 4. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

Both studies, submitted in accordance with Article 46 of Regulation (EC) No1901/2006, showed that the live attenuated rotavirus vaccine had a favourable safety profile. Neither of the two studies led the assessor to believe that there are any signals which would lead to a revision of the product's risk/benefit ratio, nor to an amendment of the safety information currently present in the vaccine's SmPC.

- **Recommendation**

No further action required.

## 5. REQUEST FOR SUPPLEMENTARY INFORMATION

Not applicable