12 March 2015
EMA/170855/2015
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 075

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

EXECUTIVE SUMMARY

This post-licensure safety study has been conducted in the Philippines to evaluate the reactogenicity and safety of the HRV vaccine Rotarix. The design is an open multi-centre study conducted in infants who received Rotarix in the course of clinical practice. Two oral doses of HRV vaccine were administered.

Study results show safety profile that is in line with the safety events observed in other studies.

This paediatric study does not influence the benefit risk for Rotarix.

No SmPC and PL changes are proposed.

1. RECOMMENDATION[1]

No further action is required.

2. INTRODUCTION

On 7 September 2012, the MAH submitted a completed paediatric study 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 does 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)

Human rotavirus RIX4414 strain (live attenuated). One dose of GSK Biologicals' lyophilised HRV vaccine contained at least 106.0 median Cell Culture Infective Dose (CCID50) of RIX4414 Live Attenuated HRV strain lyophilised with active substance: 9 mg of sucrose, 18 mg of dextran, 13.5 milligrams (mg) of sorbitol, 9 mg of amino acids, 3.7 mg of Dulbecco's Modified Eagle Medium (DMEM) reconstituted with liquid diluent containing 80 mg of calcium carbonate, 0.25% of xanthan and 1.3 mL in water for injection. As this was a PMS study, commercial lots of the vaccine that were purchased locally by the subject's parent(s)/guardian(s) were used.

Clinical aspects

1. Introduction

The MAH submitted a final report(s) for the study ROTA-043 "An open, multicentric, post-marketing surveillance study to evaluate the safety and reactogenicity of GlaxoSmithKline (GSK) Biologicals' live attenuated oral Human Rotavirus (HRV) vaccine, Rotarix when administered according to the Prescribing Information, in subjects in the Philippines aged at least 6 weeks at the time of first vaccination."

2. Clinical study

Study 103366 (ROTA-043) "An open, multicentric, post-marketing surveillance study to evaluate the safety and reactogenicity of GlaxoSmithKline (GSK) Biologicals' live attenuated oral Human Rotavirus (HRV) vaccine, Rotarix when administered according to the Prescribing Information, in subjects in the Philippines aged at least 6 weeks at the time of first vaccination."

[1] *The recommendation from section V can be copied in this section*

- **Description**

- **Methods**

  - Objective(s)

Primary:
To assess the safety and reactogenicity of GSK Biologicals' rotavirus (RV) vaccine, Rotarix.

  - Study design

A self contained, single-group (HRV group) PMS study. The participating physicians enrolled only those subjects for whom they would have prescribed Rotarix™ vaccine in the course of their normal clinical practice. All subjects were to receive two doses of Rotarix ☐ and were receive all routine vaccinations. There were 3 visits planned in this study (Visit 1 and Visit 2 for vaccination and Visit 3 for follow-up). Data collection was done using standardised hard copy Case Report Forms (CRFs).

  - Study population /Sample size

A total of 3000 subjects aged at least 6 weeks at the time of Dose 1 were planned to be enrolled over a period of 3 years, but the enrolment was stopped following the notification received from Bureau of Food and Drugs Directive (BFAD), Philippines in February 2010. As per the notification, BFAD had approved the listing of the safety data and confirmed that 1494 subjects enrolled as of February 2010 was sufficient for the study.

I.

  - Treatments

Vaccination schedule /site: Subjects were to receive two oral doses of Rotarix. The first dose was to be administered from the age of 6 weeks. There should have been an interval of at least 4 weeks between doses. The vaccination course should have been completed by the age of 24 weeks.
Vaccine composition /dose /lot number: One dose of GSK Biologicals' lyophilised HRV vaccine contained at least $10^{6.0}$ median Cell Culture Infective Dose ($CCID_{50}$) of RIX4414 Live Attenuated HRV strain lyophilised with active substance: 9 mg of sucrose, 18 mg of dextran, 13.5 milligrams (mg) of sorbitol, 9 mg of amino acids, 3.7 mg of Dulbecco's Modified Eagle Medium (DMEM) reconstituted with liquid diluent containing 80 mg of calcium carbonate, 0.25% of xanthan and 1.3 mL in water for injection. As this was a PMS study, commercial lots of the vaccine that were purchased locally by the subject's parent(s)/guardian(s) were used. Hence, lot numbers for the vaccine are not presented in the report.

  - Outcomes/endpoints

II.

Recording of solicited adverse events (AEs) (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) during the 15-day (Day 0-Day 14) follow-up period after each dose of vaccination. Recording of unsolicited AEs occurring during the 31-day (Day 0-Day 30) follow-up period after each dose of vaccination. Recording of Serious Adverse Events (SAEs) occurring during the entire study period.
Primary Endpoint:

- Occurrence of grade "2" or grade "3" fever, vomiting or diarrhoea during the 15-day (Day 0-Day 14) follow-up period after each vaccine dose.

Secondary Endpoints:

- Occurrence of solicited symptoms during the 15-day (Day 0-Day 14) solicited follow-up period after each vaccine dose.
- Occurrence of unsolicited symptoms during the 31-day (Day 0-Day 30) follow-up period after each vaccine dose, according to Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of SAEs throughout the study period.

  - Statistical Methods

Analysis of demography:
Demographic characteristics (age, gender, and race) of the study cohort were tabulated. The mean age (plus range and standard deviation) of the enrolled subjects, as a whole, was calculated at each visit. The distribution of subjects enrolled among the study sites was tabulated. The mean height, weight and body mass index (BMI) at Visit 1, of the enrolled subjects were also tabulated.

Analysis of reactogenicity and safety:
Analysis was performed only on the Total Vaccinated Cohort (TVC).
The overall incidence, with exact 95% confidence interval (CI), of any AEs (solicited or unsolicited) during the solicited follow-up period was tabulated for each dose, for overall doses and per subject.
The incidence, with exact 95% CI, of each individual solicited symptom over the solicited follow-up period, after each dose, for all doses and per subject was calculated. The same calculations were done for each individual solicited symptom rated as grade "2" and grade "3" and for each individual solicited symptom related to the vaccination. The percentage of subjects with at least one report of unsolicited AE classified by the World Health Organisation Preferred Terms (PT) or by the MedDRA, whenever available, and reported up to 30 days after vaccination was tabulated with exact 95% CI. The same tabulation was performed for grade "3" unsolicited AEs and for unsolicited AEs with a relationship to the vaccination. SAEs and withdrawal due to AEs were described in detail. The percentage (with exact 95% CI) of subjects who received concomitant medication during the solicited follow-up period after each dose, for all doses and per subject, was tabulated. Similar tabulation was done for subjects who received concomitant medication during the entire study period. The proportion of AEs resulting in a medically attended visit was tabulated.

➢ **Results**

- Recruitment/ Number analysed

1494 subjects were enrolled as of February 2010. Due to a natural calamity (typhoon), 55 out of 1494 CRFs were destroyed and no data was available for these subjects except for 1 subject (subject number 1239) for whom only the SAE forms (copies of original) were available. Therefore, these subjects were not included in the total enrolled.
The analysis was based on 1439 subjects whose data was available. Only the SAE's reported for one subject (subject number 1239) are included in the total SAEs reported in the study. Therefore, the total enrolled subjects were 1440 and TVC consisted of 1439 subjects with at least one documented dose of Rotarix™ in this study.

- Baseline data

Demography:
The mean age of the subjects in the TVC at Dose 1 was 11.2 weeks (range: 4 weeks to 38 weeks) and the mean age of the subjects at Dose 2 was 19.2 weeks (range: 10 weeks to 34 weeks). The subjects were predominantly of "East/South East Asian" origin (97.6%); 51.9% of the subjects were male and 48.1 % of the subjects were female.

- Efficacy results

Non applicable.

- Safety results

Overall:
- At least one symptom (solicited or unsolicited) was reported for 57.4% of the subjects during the 15-day (Day 0-Day 14) follow-up period. There was no increase in the incidence of AEs (solicited or unsolicited) from Dose 1 to Dose 2 of Rotarix™.
- Grade "3" symptoms (solicited or unsolicited) were reported for 8.1% of the subjects and those assessed as causally related to vaccination were reported for 13.7% of the subjects.

Primary endpoint:
- The percentage of subjects reporting grade "2" or grade "3" solicited AEs (fever, vomiting, and diarrhoea) during the 15-day (Day 0-Day 14) follow-up period was 14.7%.

Table 1: Percentage of doses and of subjects reporting grade 2 or 3 symptoms (fever, vomiting or diarrhoea) during the 15-day (Day 0-Day 14) solicited follow-up period (Total vaccinated cohort)

	Group	Any symptom				
					95% CI	
		N	n	%	LL	UL
Dose 1	HRV	1439	147	10.2	8.7	11.9
Dose 2	HRV	1304	98	7.5	6.1	9.1
Overall/dose	HRV	2743	245	8.9	7.9	10.1
Overall/subject	HRV	1439	212	14.7	12.9	16.7

HRV = Human rotavirus vaccine
For each dose and overall/subject:
N= number of subjects with at least one administered dose
n (%) = number (percentage)of subjects presenting at least one type of symptom
For overall/dose:
N= number of administered doses
n (%) = number (percentage)of doses followed by at least one type of symptom
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Secondary endpoints:
Solicited general Adverse Events:

- The most frequently reported solicited AE after each dose was irritability; reported for 32.2% and 23.5% of subjects following Dose 1 and Dose 2, respectively.
- The most frequently reported Grade 3 solicited AE was vomiting (3.1%) after Dose 1 and irritability (1.8%) after Dose 2 of HRV vaccine.
- The most frequently reported solicited AE with causal relationship to vaccination after each dose was irritability (6.9%) after Dose 1 and (5.4%) after Dose 2 of HRV vaccine.

Unsolicited Adverse Events:

- The percentage of subjects reporting at least one unsolicited AE classified by MedDRA system organ class (SOC) and PT during the 31-day (Day 0-Day 30) follow-up period was 24.5%.
- Grade “3” unsolicited AEs were reported for four subjects during the 31-day (Day 0-Day 30) follow-up period.
- Unsolicited AEs with causal relationship to vaccination were reported for 13 subjects during the 31-day (Day 0-Day 30) follow-up period.

Serious adverse events:

- There were no fatal events reported in this study. There were 41 SAEs reported by 33 subjects of which 6 SAEs reported for 4 subjects were assessed by the investigator as causally related to the vaccination.
- All the SAEs reported were resolved and the subjects recovered from these event(s), except for the 2 SAEs reported for subject number 1239 who was lost to follow-up and the status of SAEs could not be verified.
- Two SAEs (acute gastroenteritis and urinary tract infection) were reported for Subject number 1239 in the safety database but the CRF and Original SAE forms were destroyed during typhoon. These SAEs have been included in the above mentioned 41 SAEs reported by 33 subjects.

Withdrawals due to adverse events /serious adverse events:

- Seven subjects were withdrawn from the study due to unsolicited AEs or SAEs. Seven of these unsolicited AEs or SAEs (constipation, hypersomnia, hypophagia, urinary tract infection, intussusception, bloody stools and generalised rashes) experienced by five subjects were considered by the investigator to be causally related to the vaccination.

3. Discussion on clinical aspects

This study was conducted to collect the additional safety data on GSK Biologicals’ Rotarix vaccine in the local target population, as per the requirements of BFAD, in the Philippines.

Among solicited AE with causal relationship to vaccination in the 15-day follow-up period, irritability was the most frequently reported in this study, in 6.9% and 5.4% of subjects following dose 1 and dose 2, respectively. In the integrated safety analysis of seven clinical trials, which included 3,286 HRV

vaccine recipients, the MAH observed that fussiness/irritability was the most frequently reported solicited general symptom during the 8-day post-vaccination period after each dose [Cheuvart, 2009].

In this study, at least one unsolicited AE was reported for 24.5% subjects within the 31-day follow-up period after each vaccination. The integrated safety summary of unsolicited AEs included 5082 infants in the HRV vaccine group from seven studies and at least one unsolicited AE of any intensity occurring within the 31-day post-vaccination period after each dose was reported for 53.31% of infants [Cheuvart, 2009].

During the entire study period, SAES were reported for 2.2% subjects and 6 over the 33 SAEs were assessed by the investigators as causally related to the vaccination and 0.5% subjects withdrew from the study due to unsolicited AEs. The integrated safety summary of SAEs included 36,755 infants in the HRV vaccine group from eight studies and at least one SAE was reported by 2,219 (6.04%) of subjects. The number and percentage of infants discontinuing the study because of non-serious AEs or SAEs was 159 subjects (0.43%) [Cheuvart, 2009].

There were no fatal events reported in this study. Overall, GSK Biologicals' HRV vaccine is well tolerated in Filipino infants when administered following prescribing information. No safety concerns were raised based on the available data.

4. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The safety reports from this study are in line with those reported in the integrated safety database of the MAH. No fatal events reported in this study. Out of the 1439 subjects, one intussusception case was reported among the 1439 subjects, as well as one case of hematochezia.

In this study, a number of 3000 subjects were planned to be enrolled over a period of 3 years. As a part of the centres were destroyed in a typhoon and a number of others were unable to recruit subjects, only 1494 subjects were enrolled after more than three years. Recruitment was stopped when the Drugs Agency of the Philippines considered that this sample was sufficient for the study.

Overall, Rotarix is well tolerated in Filipino infants. No new safety concerns were raised based on the available data.

- **Recommendation**

No further action required.

5. REQUEST FOR SUPPLEMENTARY INFORMATION

None.