22 December 2014
EMA/108671/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Rotarix

International non-proprietary name: human rotavirus, live attenuated

Procedure No. EMEA/H/C/000639/P46 081

Note

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

Table of contents

1. Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

Final study report for Study DTPa-HBV-IPV-118 PRI (EUDRA CT 2013-003428-34), a standalone study where Rotarix is co-administered. The report is being submitted to comply with the requirements of Article 46 of Regulation (EC) No 1901/2006.

Further review of the submitted data, the rapporteur is of the opinion that no changes to the SmPC for *Rotarix* are required and no variation should be submitted.

1.1. Steps taken for the assessment

Submission date:	05/05/2014
Start of procedure:	23/11/2014
CHMP Rapporteur's preliminary assessment report circulated on:	23/12/2014
CHMP Rapporteur's updated assessment report circulated on:	12/01/2015
CHMP outcome:	22/01/2015

2. Assessment of the post-authorisation measure PAM

2.1. Introduction

Study DTPa-HBV-IPV-118 PRI assesses the immunogenicity and safety of GSK combined DTPa-HBV-IPV/HiB vaccine (*Infanrix™ hexa)* administered as a three-dose primary vaccination course at 2, 4 and 6 months of age in healthy infants in Canada. *Rotarix* was not specifically studied and no immunogenicity results for *Rotarix* were generated in this study.

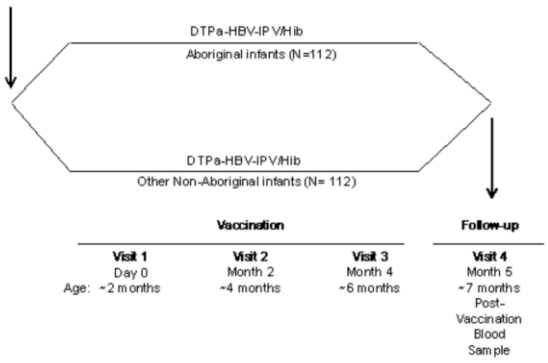
According to the *Rotarix* Product Information, *Rotarix* can be administered at the same time as other recommended vaccines, such as Hib, diphtheria, tetanus, pertusis, oral or inactivated polio, hepatitis B vaccines as well as pneumococcal and meningoccal serogroup C conjugate vaccines. The MAH has reviewed the results of this study and has concluded that no changes to the Product Information are needed.

2.2. Study design

Study Objectives: The primary objective was to assess the immune response to the Hib component of DTPa-HBV-IPV/Hib in terms of seroprotection rates one month after a three-dose primary vaccination course in "Aboriginal Infants" and "Non Aboriginals Infants".

The secondary objective were (i) to assess the response to Hib component of DTPa-HBV-IPV/Hib in terms of anti-polyribosyl-ribitol phosphate (PRP) GMCs one month after the three-dose primary vaccination, (ii) to assess the immune response to the hepatitis B components of DTPa-HBV-IPV/Hib in terms of seroprotection rates and anti-HBs GMCs one month after the three-dose primary vaccination course, and (iii) assess safety of DTPa-HBV-IPV/Hib in terms of medically attended adverse events and serious adverse events during the three-dose primary vaccination course.

Study Design: Phase IV, non-randomised, open-label study conducted in 3 centres in Canada.



There were two parallel groups, (i) "Aboriginal Infants" which included infants of the Canadian First Nation, Metis and Inuit people and (ii) "Non-Aboriginal Infants" which included infants exclusive of Aboriginals.

This was a self-contained study. The Non-Aboriginal infants" group served as control for evaluating the response to the vaccine in the Aboriginal infants" group. Blood sample was collected from all subjects one month after the third dose of the primary vaccination.

All subjects were to receive three doses of DTPa-HBV-IPV/Hib at 2, 4, and 6 months of age and two doses of *Rotarix* (lyophilised or liquid formulation) at 2 and 4 months of age, as well as pneumococcal conjugate vaccine according to the recommended provincial infant immunisation schedules.

Study Population: Healthy infants between and including 6 and 12 weeks of age at the time of the first vaccination and born after a gestation period of minimum 36 weeks. Subjects with evidence of previous or intercurrent diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B and/or Hib vaccination or disease were excluded from the study.

Study period: From September 2008 to November 2013 (date of database freeze)

Study endpoints:

Primary Outcome/Efficacy Variable:

- Immunogenicity one month after the third dose of primary vaccination course:
  - Anti-PRP antibody concentrations ≥ 0.15 µg/ml.

Secondary Outcome/Efficacy Variable(s):

- Immunogenicity one month after the third dose of primary vaccination course:
  - Anti-PRP antibody concentration ≥ 1 µg/ml.
  - Anti-HBs antibody concentration ≥ 10 mIU/ml and ≥ 100 mIU/ml
  - Anti-PRP and anti-HBs antibody concentrations.

Secondary Outcome/Safety Variable(s):

- Occurrence of medically attended adverse events and serious adverse events. An adverse event requiring medical attention is defined as:
  - a visit to or from medical personnel (doctor of medicine or nurse practitioner) for any reason (excluding scheduled study visits);
  - an emergency room visit; or
  - any serious adverse event including hospitalisation and death.

Statistical methods:

The primary analysis was based on the ATP cohort for analysis of immunogenicity and safety. An analysis on the Total Vaccinated cohort was to be performed to complement the ATP analysis only if

more than 5% of the subjects with available immunogenicity data were excluded from the ATP cohort for analysis of immunogenicity.

Safety

- The verbatim reports of medically attended AEs were reviewed by a physician and the signs and symptoms were coded according to Medical Dictionary for Regulatory Activities (MedDRA). Every verbatim term was matched with the appropriate Preferred Term. The percentage of subjects with AEs that required medical attention occurring within 31 days (Day 0 to Day 30) with its exact 95% CI was tabulated by preferred term for each study group.
- The percentage of subjects who started to receive at least one concomitant medication (i.e. any medication, antipyretic medication, prophylactic antipyretics) during the 31-day follow-up period after vaccination was tabulated with exact 95% CI.
- Concomitant vaccinations received during the course of the study were tabulated.
- Serious adverse events and withdrawals due to AEs and SAEs following vaccination were described in detail.

2.3. Results

Study Population:

Table 1 Study Population (Total Vaccinated Cohort)

Number of subjects	**Aboriginal Infants**	**Non-Aboriginal Infants**
Planned, N	112	112
N (Total Vaccinated Cohort)	112	112
Completed, n(%)	105 (93.8)	112 (100)
Demographics	**Aboriginal Infants**	**Non-Aboriginal Infants**
N (Total Vaccination Cohort)	112	112
Females:Males	62:50	52:60
Mean Age, weeks (SD)	9.3 (1.38)	9.2 (1.30)
Aboriginal, n(%)	111 (99.1)	
White – Caucasian / European heritage, n(%)		64 (57.1)

Immunogenicity

Table 2 Seroprotection rates and GMCs for anti-PRP antibodies one month after the third vaccine dose by groups (ATP cohort for immunogenicity)

				≥ 0.15 µg/ml				**≥ 1 µg/ml**				**GMC**		
						95% CI				**95% CI**			**95% CI**	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti-PRP	Aboriginal	Post-Pri*	94	92	97.9	92.5	99.7	83	88.3	80.0	94.0	6.123	4.498	8.334
	Non-Aboriginal	Post-Pri	107	106	99.1	94.9	100	91	85.0	76.9	91.2	3.510	2.745	4.488

*: Post-Pri = Post primary blood sampling time point

Table 3 Seroprotection rates, percentage of subjects with antibody concentrations greater than or equal to 100 mIU per ml and GMCs for CLIA anti-HBs antibodies, one month after the third vaccine dose by groups (ATP cohort for immunogenicity)

		≥ 10 mIU/ml				≥ 100 mIU/ml				GMC		
				95% CI				95% CI			95% CI	
Group	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Aboriginal	91	91	100.0	96.0	100.0	88.6	97.4	91.5	99.9	1797.9	1375.1	2350.7
Non-Aboriginal	103	103	100.0	96.5	100.0	100.2	97.3	91.9	99.8	1544.4	1210.4	1970.5

Assessor's comment: *The number of subjects with antibody concentrations ≥ 100 mIU per ml is not round and the table should be corrected for those values.*

Safety /reactogenicity:

- At least one unsolicited symptom that required medical attention during the 31-day follow-up period after vaccination was reported for 23.2% and 17.0% of subjects in Aboriginal Infants and Non-Aboriginal Infants groups.
- In the Aboriginals Infants, pyrexia (5.4%) was the most commonly reported unsolicited symptom that required medical attention followed by bronchiolitis and otitis media (both 3.6%). In the Non-Aboriginal Infants, eczema (2.7%) was most commonly reported followed by bronchiolitis, otitis media and respiratory syncytial virus infection (all three 1.8%).

Serious adverse events:

- SAEs were reported for six subjects in the Aboriginal Infants group during the entire study period. Two SAEs were reported after dose 1, three SAEs were reported after dose 2 and one SAE was reported after dose 3. All the SAEs were recovered/resolved by the end of the study.
- One SAE (Pyrexia) reported for a subject was assessed by the investigator as causally related to the study vaccine. This SAE was reported immediately after the administration of the dose 1 and this warranted an emergency room visit. This SAE resolved in 2 days.
- No fatal SAEs were reported in the study.

Table 4 Listing of SAEs (Total vaccinated cohort)

Group	Sub. No.	Case Id	Age at onset (Week)	Sex	Verbatim	Preferred term	System Organ Class	MA type	Dose	Day of onset	Duration	Intensity	Causality	Outcome
Aboriginal Infants	3	R0002698A	24	F	Bronchiolitis	Bronchiolitis	Infections and infestations	HO	2	38	3	3	N	Recovered/resolved
	153	R0003495A	9	F	Fever	Pyrexia	General disorders and administration site conditions	ER	1	0	2	2	Y	Recovered/resolved
	182	R0006523A	15	F	Seizures	Convulsion	Nervous system disorders	HO	1	36	1	3	N	Recovered/resolved
	192	R0009137A	23	F	Febrile seizure	Febrile convulsion	Nervous system disorders	HO	2	39	4	3	N	Recovered/resolved
	197	R0010618A	25	M	Bacterial pneumonia	Pneumonia bacterial	Infections and infestations	HO	2	45	18	2	N	Recovered/resolved
			25		Respiratory syncytial virus infection	Respiratory syncytial virus infection	Infections and infestations	HO	2	45	16	2	N	Recovered/resolved
	452	R0018042A	33	M	Seizure - possible	Convulsion	Nervous system disorders	MC	3	44	1	1	N	Recovered/resolved

Withdrawals due to adverse events /serious adverse events: None

2.4. Conclusion:

- One month after the primary vaccination with *Infanrix™ hexa*, anti-PRP seroprotection levels were seen in 97.9% of subjects in the Aboriginal Infants group and in 99.1% of subjects in the Non-Aboriginal Infants group.
- Anti-PRP GMCs were 6.123 µg/ml (95% CI: 4.498-8.334) in the Aboriginal Infants group and 3.510µg/ml (95% CI: 2.745-4.488) in the Non-Aboriginal Infants group.
- One month after the primary vaccination with *Infanrix hexa*, seroprotective anti-HBs antibody concentration ≥10 mIU/mL was observed in 100% of subjects in Aboriginal Infants and Non-Aboriginal Infants and antibody concentration ≥100 mIU/mL was observed in 97.4% and 97.3% of subjects in Aboriginal Infants and Non-Aboriginal Infants groups, respectively.
- The anti-HBs GMCs were 1797.9 mIU/mL (95% CI: 1375.1- 2350.7) and 1544.4 mIU/mL (95% CI: 1210.4-1970.5) for Aboriginal Infants and Non-Aboriginal Infants groups, respectively.
- No confirmatory analyses were performed on the primary and secondary objectives.
- At least one unsolicited symptom that required medical attention during the 31-day follow-up period after vaccination was reported for 23.2% and 17.0% of subjects in Aboriginal Infants and Non-Aboriginal Infants groups, respectively.
- SAEs were reported for six subjects in the Aboriginal Infants group during the entire study period. One SAE (pyrexia) was assessed by the investigator as causally related to the study vaccine. All the SAEs were recovered/resolved by the end of the study. No fatal SAEs were reported.
- In this study, the study vaccine was generally well tolerated.

3. Rapporteur's overall conclusion

No data on the immunogenicity of *Rotarix* was provided in this report.

Study DTPa-HBV-IPV-118 PRI was not designed to exclude an effect of *Rotarix* on the immunogenicity and safety of DTPa-HBV-IPV/Hib vaccine in health infants. Those results are not unexpected and do not modify the current knowledge on the vaccine.

☒ PAM fulfilled (all commitments fulfilled) - No further action required