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EMA/149930/2013
Committee for Medicinal Products for Human Use (CHMP)

Infanrix hexa

(diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) and haemophilus influenzae type b (hib) conjugate vaccine (adsorbed))

Procedure No. EMEA/H/C/000296/P46/0105

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

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

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I. EXECUTIVE SUMMARY

SmPC and PL changes in section 5.1 will be proposed by the MAH in due time.

II. RECOMMENDATION[1]

The MAH has submitted the results of an open, phase IV, multicentre study to assess the long-term persistence of antibodies against hepatitis B and the immune response to a hepatitis B (*Engerix-B Kinder*) vaccine challenge in children aged 7–8 years, previously primed and boosted in the first two years of life with GlaxoSmithKline (GSK) Biologicals' DTPa-HBV-IPV/Hib (*Infanrix hexa*) vaccine (Study No. 112688 (DTPA-HBV-IPV-113)).

The results of this study warrant a change in section 5.1 of the SmPC.

III. INTRODUCTION

In the global context of vaccination against hepatitis B, the European Medicines Agency had requested that GSK Biologicals set up a long-term surveillance programme of vaccines containing a recombinant hepatitis B component. This study is post-approval commitment study for *Infanrix hexa.*

In Germany, GSK Biologicals' hepatitis B vaccine, *Engerix-B,* is licensed and marketed under the trade name *Engerix-B Kinder*.

This study is the second of a series of four studies, constituting a common follow-up programme of vaccination with *Infanrix hexa* which aimed to determine the persistence of hepatitis B immunity, from childhood to adolescence resulting from infant vaccination with *Infanrix hexa*. Persistent immunity to hepatitis B was to be assessed successively in different cohorts aged five, eight, twelve and fifteen years, who received four consecutive doses of *Infanrix hexa* as primary and booster vaccination. These studies are being conducted in Germany.

The 5-year-old cohort study was completed in 2007 (Steiner et al. 2010), the 8-year-old cohort of vaccinees was assessed in the current study and the recruitment for the 12-year and 15- year age groups will be performed when the cohort of *Infanrix hexa* vaccinees reach the target age for enrolment.

On 3 July2012, the MAH submitted a completed paediatric study for Infanrix Hexa, 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 Infanrix Hexa and that there is no consequential regulatory action. However, the MAH has concluded that an update of the SmPC is deemed necessary and will submit an update of section 5.1 in due date.

IV. SCIENTIFIC DISCUSSION

IV.1 Clinical aspects

1. Introduction

The MAH submitted a final report(s) for Study No. 112688 (DTPA-HBV-IPV-113).

2. Clinical study

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

Study No. 112688 (DTPA-HBV-IPV-113)

- **Description**

The MAH submitted the results for the following study: an open, phase IV, multicentre study to assess the long-term persistence of antibodies against hepatitis B and the immune response to a hepatitis B (*Engerix-B Kinder*) vaccine challenge in children aged 7–8 years, previously primed and boosted in the first two years of life with GlaxoSmithKline (GSK) Biologicals' DTPa-HBV-IPV/Hib (*Infanrix hexa*) vaccine. There was only one study group, the Hexa Group, and a single dose of HBV vaccine was administered to all subjects who were previously primed and boosted with four doses of *Infanrix hexa* in the first two years of life.

This study was conducted across 12 centres in Germany.

- **Methods**

- Objective(s)

Primary Objective

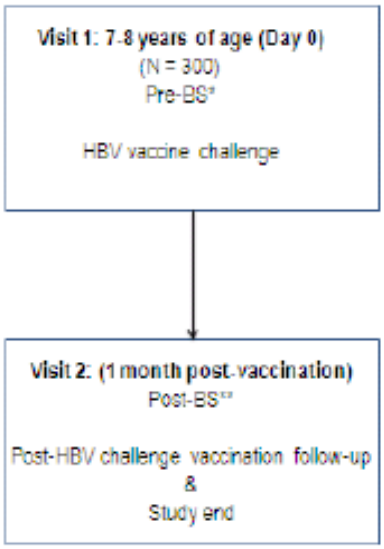
- To assess the anti-HBs antibody response to a challenge dose of HBV vaccine (*Engerix-B Kinder*) in subjects 7–8 years of age, previously vaccinated with four doses of *Infanrix hexa* in the first two years of life.

Secondary Objective

- To assess the persistence of anti-HBs antibodies in subjects 7–8 years of age, previously vaccinated with four doses of *Infanrix hexa* in the first two years of life.
- To evaluate the safety and reactogenicity of a challenge dose of HBV vaccine (*Engerix-B Kinder*) in terms of solicited symptoms (local and general), unsolicited symptoms and serious adverse events (SAEs) during the study period.

- Study design

An open-label, phase IV, single-group, non-randomised, multicentre study. Two blood samples were drawn: one before, and the other, one month after the challenge dose of HBV vaccine.



N: Number of subjects planned to be enrolled
BS: Blood sampling
*: Blood sampling before the administration of the HBV vaccine challenge
**: Blood sampling one month after the administration of the HBV vaccine challenge

- Study population /Sample size

A healthy male or female 7 to 8 years of age (from and including the 7th birthday up to, but excluding the 9th birthday) at the time of enrolment, with documented evidence of previous vaccination with *Infanrix hexa* that included three doses of primary vaccination received by nine months of age and one booster dose received between 11 and 18 months of age. Subjects with written informed consent obtained from the parent(s)/legally acceptable representative [LAR(s)] of the subject and with written informed assent from the subject, if applicable at the time of enrolment were included in the study. The evidence of previous hepatitis B booster vaccination since administration of the fourth dose of *Infanrix hexa* booster in the second year of life, history of, or intercurrent hepatitis B disease and hepatitis B vaccination at birth excluded subjects from the study.

The primary objective of the study was to assess if the anti-HBs antibody response to a challenge dose of HBV vaccine was above 90%. A total of 300 children aged 7–8 years, who received four doses of *Infanrix hexa* in the first two years of life, were enrolled in this study. It was assumed that 10% of subjects enrolled in this study might have been non-evaluable at the time of the analysis (e.g., drop-outs, non-compliance with protocol, etc.). A sample size of 270 evaluable subjects provides a power of at least 86% for the lower limit of the 95% confidence interval (CI) for the percentage of subjects who have responded to the HBV vaccine challenge (i.e. anti-HBs antibody concentrations ≥ 100 mIU/ml one month after HBV vaccine challenge) to be more than 90%, if the true percentage of subjects who have responded to the HBV vaccine challenge is 95%, as shown in Table 8 (of the study report, not shown here).

- Treatments

A single dose of HBV vaccine, *Engerix-B Kinder* was administered to all subjects as an intramuscular (IM) injection into the deltoid region of the non-dominant arm.

- Outcomes/endpoints

Primary Outcome:

Immunogenicity: Immunogenicity with respect to the components of the study vaccine.

- Subjects with antibodies to hepatitis B surface antigen (anti-HBs) antibody concentrations ≥ 100 mIU/ml, one month after the challenge dose of HBV vaccine

Secondary Outcome:

Immunogenicity:

- Anti-HBs antibody persistence after previous vaccination with *Infanrix hexa*.
  - Distribution of subjects with anti-HBs antibody concentrations ≥ 3.3 mIU/ml, ≥ 10 mIU/ml, 10 to < 100 mIU/ml, ≥ 100 mIU/ml and anti-HBs geometric mean concentration (GMC), before the challenge dose of HBV vaccine.
- Immunogenicity with respect to the components of the study vaccine.
  - Distribution of subjects with anti-HBs antibody concentrations ≥ 3.3 mIU/ml (seropositive titer), ≥ 10 mIU/ml (seroprotective titer) and anti-HBs GMC, one month after the challenge dose of HBV vaccine.
  - Anamnestic response to the HBV challenge dose, which was defined as:
    At least (i.e. greater than or equal to) a 4-fold rise in anti-HBs antibody concentrations post-HBV challenge dose in subjects seropositive at the pre-challenge dose time-point. Anti-HBs antibody concentrations ≥ 10 mIU/ml post-HBV challenge dose in subjects seronegative at the pre-challenge dose time-point.

Safety and reactogenicity:

- Solicited local and general symptoms: Occurrence of each solicited local and general symptom during the 4-day (Day 0–Day 3) follow-up period after the challenge dose of HBV vaccine.
- Unsolicited adverse events (AEs): Occurrence of unsolicited AEs during the 31-day (Day 0–Day 30) follow-up period after the challenge dose of HBV vaccine.
- Serious adverse events: Occurrence of SAEs after the challenge dose of HBV vaccine up to study end.

- Statistical Methods

Analyses were performed as specified in the protocol and in the study reporting and analysis plan (RAP).

➢ Results

- Recruitment/ Number analysed

Study population (Total Vaccinated cohort)	
Number of subjects	**Hexa Group**
Planned, N	300
Randomised, N (Total Vaccinated cohort)	297
Completed, n (%)	297 (100)
Demographics	**Hexa Group**
N (Total Vaccinated cohort)	297
Females: Males	144:153
Mean Age, years (SD)	7.5 (0.52)
White-Caucasian/European heritage, n (%)	295 (99.3)
Hexa Group = Subjects who received a single dose of HBV vaccine in this study and were previously primed and boosted with four doses of *Infanrix hexa* in the first two years of life N = total number of subjects, n = number of subjects in a given category, SD = Standard deviation	

- Efficacy results

The primary analysis of immunogenicity was performed on the ATP cohort for immunogenicity. An analysis on the Total Vaccinated cohort was not performed to complement the ATP analysis

since not more than 5% of the subjects with available immunogenicity data were excluded from the planned ATP cohort for immunogenicity.

Primary outcome

One month after the challenge dose of HBV vaccine, 97.5% of subjects had anti-HBs antibody concentrations ≥ 100 mIU/ml.

Secondary outcome

Persisting seroprotective (≥ 10 mIU/ml) anti-HBs antibody concentrations were observed in 80.5% of children aged 7 to 8 years who were vaccinated in infancy with four doses of *Infanrix hexa* in routine clinical practice.

Anti-HBs seropositivity rates, percentage of subjects with antibody concentrations ≥ 10 mIU/ml, percentage of subjects with antibody concentrations ≥ 100 mIU /ml and GMCs (calculated on all subjects) at pre and post challenge dose time-point (ATP cohort for immunogenicity)

Timing	N	≥ 3.3 mIU/ml				≥ 10 mIU/ml				≥ 100 mIU/ml				GMC		
		n	%	95% CI		n	%	95% CI		n	%	95% CI		Value	95% CI	
				LL	UL			LL	UL			LL	UL		LL	UL
Pre	284	254	89.4	85.3	92.8	229	80.6	75.6	85.1	101	35.6	30.0	41.4	52.3	41.8	65.5
Post	284	282	99.3	97.5	99.9	282	99.3	97.5	99.9	277	97.5	95.0	99.0	8792.5	6966.0	11097.8

N = number of subjects with available results, n (%) = number (percentage) of subjects with concentration within the specified range, 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit, GMC = geometric mean concentration calculated on all subjects, Pre = Pre challenge dose time-point, Post = Post challenge dose time-point

An anamnestic response to the hepatitis B challenge dose was mounted by 97.2% of subjects.

- Safety results

The safety analysis was performed on the Total Vaccinated cohort.

- *Any Symptom:* During the 4-day post-challenge dose follow-up period at least one symptom (solicited or unsolicited, local or general) was reported for 56.2% of subjects.
- *Solicited local symptoms*: Pain at the injection site was the most frequent solicited local symptom (reported for 30.6% of subjects). Pain of Grade 3 intensity was reported for two subjects.
- *Solicited general symptoms:* Fatigue and headache were the most frequent solicited general symptom (reported for 12.5% and 12.1% of subjects, respectively). Gastrointestinal symptoms of Grade 3 intensity were reported for five subjects.
- *Unsolicited symptoms:* At least one unsolicited symptom was reported for 14.1% of subjects during the 31-day (Day 0-Day 30) follow up period. Abdominal pain of Grade 3 intensity was reported for one subject. One subject experienced injection site haematoma that was considered by the investigator to be causally related to vaccination.
- *Serious adverse events*: Two subjects experienced three SAEs during the study period which resolved by the end of the study. None of these SAEs were considered by the investigator to be causally related to the vaccination. No fatal events were reported during the study.
- *Withdrawals due to AEs /SAEs*: None of the subjects were withdrawn due to an AE or SAE during the study period.

3. Discussion on clinical aspects

- In children routinely primed and boosted in infancy with four doses of *Infanrix hexa*, seroprotective anti-HBs antibody concentrations were still observed in 80.5% of subjects at 7 to 8 years of age.
- One month after a challenge dose of HBV vaccine, 97.5% of subjects had anti-HBs antibody concentrations ≥100 mIU/ml and 97.2% of subjects displayed an anamnestic response.

- The challenge dose of HBV vaccine was generally well tolerated. Unsolicited symptoms were reported for 14.1% of subjects during the 31-day follow-up period. Three SAEs were reported during the study, which were not considered by the investigator to be causally related to the vaccination, and were resolved by the end of this study.
- These results are consistent with previous observations in another study conducted in the same country and in the same age group (Zinke et al. 2009).

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➢ **Overall conclusion**

Infanrix Hexa was licensed in 2000 in Europe for the primary immunisation of children against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive infections caused by Haemophilus influenzae b. The current study was performed to assess the quality of the long-term immunogenicity of the Hepatitis B component of the vaccine by characterisation of the anti-HB antibody persistence and the anamnestic response (following HB vaccine administration) in children 7-8 years previously primed and boosted in the first two years of life with Infanrix Hexa. Protection against HB is dependent on seroprotective antibody titres and the individual's capacity to mount an anamnestic response upon HB infection.

The data presented in the current report that in the subjects under study, 80% displays seroprotective anti-HB antibody titers in children 7-8 years following infant immunisation. One month following HB challenge, 99% of the individuals displayed seroprotective titres and in 97% an anamnestic response was demonstrated fulfilling the criteria set for such response. Altogether, these data demonstrate that the immunogenicity of the HB component of the Infanrix Hexa vaccine, when administered according to the infant immunisation schedule, results in adequate protection until at least the age of 7-8 years.

Similar results as presented in this report have been published in the same or younger age groups (Zinke et al. 2009; Steiner et al. 2010; Zanetti et al. 2010).

➢ **Recommendation**

A Type II variation will be submitted by the MAH in due time.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

Not applicable

VII. REFERENCES

Steiner, M., Ramakrishnan, G., Gartner, B., Der Meeren, O. Van, Jacquet, J.-M., and Schuster, V. (2010). Lasting immune memory against hepatitis B in children after primary immunization with 4 doses of DTPa-HBV-IPV/Hib in the first and 2nd year of life. BMC infectious diseases 10, 9.

Zanetti, A. R. et al. (2010). Hepatitis B immune memory in children primed with hexavalent vaccines and given monovalent booster vaccines: an open-label, randomised, controlled, multicentre study. The Lancet infectious diseases 10, 755-61.

Zinke, M. et al. (2009). Immune memory to hepatitis B virus in 4-9-year old children vaccinated in infancy with four doses of hexavalent DTPa-HBV-IPV/Hib vaccine. Human vaccines 5, 592-8.