22 March 2018
EMA/216598/2018
Human Medicines Evaluation Division

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

Infanrix hexa

International non-proprietary name: 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/P46/128

Note

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

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1. Introduction

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

The European Medicines Agency has requested GlaxoSmithKline (GSK) Biologicals to set up a long-term surveillance programme of vaccines containing a recombinant hepatitis B component. This study is the fourth in a series of four, constituting a common immunological follow-up program after vaccination with Infanrix hexa.

1.1. Steps taken for the assessment

Submission date:	14/12/2018
Start of procedure:	22/01/2018
CHMP Rapporteur's preliminary assessment report circulated on:	26/02/2018
CHMP Rapporteur's updated assessment report circulated on:	22/03/2018
CHMP opinion:	22/03/2018

2. Assessment of the post-authorisation measure Article 46 on DTPa-HBV-IPV-115

A phase IV, open-label, multicentre study to assess the long-term persistence of antibodies against hepatitis B and the immunogenicity and safety of a challenge dose of hepatitis B vaccine (Engerix-B Kinder SKF103860) in children aged 14-15 years, previously primed and boosted in the first two years of life with four doses of GSK Biologicals' DTPa-HBV-IPV/Hib (Infanrix hexa SB217744) vaccine.

The European Medicines Agency has requested GSK Biologicals to set up a long-term surveillance programme of vaccines containing a recombinant hepatitis B component. This study is the fourth in a series of four, constituting a common immunological follow-up program after vaccination with Infanrix hexa. The three previous studies in this series are mentioned below:

- 106789 (DTPA-HBV-IPV-112): The study population was healthy subjects of 4-5 years of age at the time of enrolment, who had four consecutive doses of Infanrix hexa. The study report date is 04 December 2008.
- 112688 (DTPA-HBV-IPV-113): The study population was healthy subjects of 7-8 years of age at the time of enrolment who had four consecutive doses of Infanrix hexa. The study report date is 28 March 2012 and the study report amendment 1 date is 24 February 2014.
- 106793 (DTPA-HBV-IPV-114): The study was conducted in healthy subjects 12-13 years of age at the time of enrolment who received four consecutive doses of Infanrix hexa. The study report date is 17 August 2015.

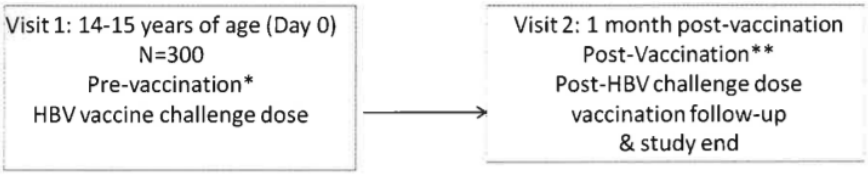
This study aimed to determine the persistence of immunity to hepatitis B, from childhood to adolescence that is conferred by four doses of vaccination with Infanrix hexa in the first 2 years of age. Persistent immunity to hepatitis B was assessed previously, in 4-5 years old, 7-8 years old and 12-13 years old, respectively who were vaccinated with four doses of Infanrix hexa, as part of routine vaccination in infancy, in Germany. More than 60% of subjects showed seroprotective persistent antibody concentrations and at least 96% of subjects in all age groups showed an anamnestic response to the single hepatitis B challenge dose [Zinke, 2010, Steiner, 2010; Van Der Meeren, 2014; Behre, 2016]. The results observed in these studies are in line with the results observed when children and adolescents were primed with three doses of a monovalent hepatitis B vaccine [Van Der Meeren, 2016; Behre, 2012].

Infanrix hexa was licensed for use in Germany in 2000. Thus, children who received routine vaccination in the year 2001 with Infanrix hexa had reached the age of 14 to 15 years by 2016. These children were invited to participate in this study to collect persistence data for hepatitis B antibodies and to assess the anamnestic response, immunogenicity, safety and reactogenicity of a single challenge dose of the hepatitis B vaccine (Engerix-B Kinder).

Study Design

A phase IV, open-label, multicentre study to assess the long-term persistence of antibodies against hepatitis B and the immunogenicity and safety of a challenge dose of hepatitis B vaccine (Engerix-B Kinder SKF103860) in children aged 14-15 years, previously primed and boosted in the first two years of life with four doses of GSK Biologicals' DTPa-HBV-IPV/Hib (Infanrix hexa SB217744) vaccine. A total of 302 subjects were vaccinated and all completed the study and 268 subjects were included in the ATP cohort for analysis of the immunogenicity. The persistence of anti-HBs antibody

concentrations in subjects 14-15 years of age previously vaccinated with four doses of Infanrix hexa in the first two years of life was evaluated in this study.



N: Number of subjects planned to be enrolled
* Pre-vaccination: Blood sampling before the administration of the single HBV vaccine challenge dose
** Post-vaccination: Blood sampling one month after the administration of the single HBV vaccine challenge dose

Objectives

Primary objective

- To assess the immunological response to hepatitis B surface antigen (anti-HBs), in terms of antibody concentrations ≥100 mIU/mL, one month after the single challenge dose of the HBV vaccine in subjects 14-15 years of age, previously vaccinated with four doses of Infanrix hexa in the first two years of life.

Secondary objectives

- To assess the persistence of anti-HBs antibodies, in terms of seroprotection status and antibody concentrations, in subjects 14-15 years of age, previously vaccinated with four doses of Infanrix hexa in the first two years of life.
- To assess the immunological response to hepatitis B surface antigen, in terms of anamnestic response, one month after the single challenge dose of the HBV vaccine in subjects 14-15 years of age, previously vaccinated with four doses of Infanrix hexa in the first two years of life.
- To assess the immunological response to the hepatitis B surface antigen, in terms of seroprotection status and antibody concentrations, one month after the single challenge dose of the HBV vaccine in subjects 14-15 years of age, previously vaccinated with four doses of Infanrix hexa in the first two years of life.

Analysis of the study

Immunogenicity results

- One month after the challenge dose of HBV vaccine, 87.3% of the subjects had anti-HBs antibody concentrations ≥ 100 mIU/mL and the anti-HBs GMC was 1975.7 mIU/mL (95% CI: 1436.1–2718.1).
- Persisting seroprotective anti-HBs antibody concentrations (i.e. anti-HBs antibody concentrations ≥ 10 mIU/mL) were observed in 53.7% of the children aged 14 to 15 years who were vaccinated in infancy with four doses of Infanrix hexa in routine clinical practice. Refer to Table 1.
- One month after the challenge dose, 93.3% reached seroprotective anti-HBs antibody concentrations ≥ 10 mIU/ml.
- An anamnestic response to the hepatitis B challenge dose was mounted by 92.5% of the subjects.

Table 1: Percentage of subjects with antibody concentrations ≥ 6.2 mIU/mL, ≥ 10 mIU/mL, ≥ 100 mIU/mL and GMCs for anti-HBs antibody concentrations at pre-challenge dose and one month after the challenge dose (ATP cohort for analysis of immunogenicity)

			≥ 6.2 mIU/mL				≥ 10 mIU/mL				≥ 100 mIU/mL				GMC		
					95% CI				95% CI				95% CI			95% CI	
Group	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
HBV	Pre	268	163	60.8	54.7	66.7	144	53.7	47.6	59.8	45	16.8	12.5	21.8	15.6	12.8	19.1
Group	P1(D30)	268	255	95.1	91.8	97.4	250	93.3	89.6	96.0	234	87.3	82.7	91.1	1975.7	1436.1	2718.1

HBV Group = Subjects who previously received 4 doses of *Infanrix hexa* in first two years of life and received a challenge dose of HBV vaccine in this study
GMC = geometric mean antibody concentration calculated on all subjects
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
Pre: Blood sampling at pre-challenge dose time point
P1(D30): Blood sampling one month after the challenge dose
Source: Table 14.2.1.2

Safety results

- Any Symptom: During the 4-day post-challenge dose follow-up period, at least one adverse event (solicited or unsolicited, local or general) was reported for 65.6% of the subjects.
- Solicited local symptoms: Pain at the injection site was the most frequently reported solicited local symptom (reported for 33.6% of the subjects) and also the only Grade 3 solicited local symptom reported at the injection site (reported for 1.0% of the subjects).
- Solicited general symptoms: Fatigue was the most frequently reported solicited general symptom (reported for 30.2% of the subjects). The most frequently reported Grade 3 solicited general symptom was headache (reported for 4.3% of the subjects).
- Unsolicited adverse events: At least one unsolicited adverse event was reported for 18.2% of the subjects during the 31-day (Day 0-Day 30) follow up period. At least one unsolicited adverse event of Grade 3 intensity was reported for 2.3% of the subjects. The following unsolicited adverse events were considered by the investigator to be causally related to vaccination: dizziness (reported for 0.7 % of subjects) and injection site pruritus, malaise, pain and pain in extremity (each reported for 0.3% of subject).
- Serious adverse events: Two SAEs were reported during the study (meniscus injury and eating
  disorder). Neither of these SAEs was considered by the investigator to be causally related to the vaccination and both had resolved by the end of the study. No fatal SAEs were reported during the study.
- Withdrawals due to AEs /SAEs: None of the subjects were withdrawn from the study due to an AE or SAE during the entire study period.

The Company concluded that these different results justify an update of the information on the persistence for protection in the PI as they may be relevant to the prescribers. No new safety issues.

3. Rapporteur's overall conclusion

The Rapporteur agrees and endorses the discussion. MS1 commented on the lower boosterability of the subjects than seen in previous studies (see below) and the Rapporteur endorses their comments. The MAH will submit a variation type II to update the SmPC with the Hepatitis B persistence of protection. No further actions are required and the PAM is considered fulfilled.

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

MS1 comments

MS1 endorse the conclusion of the rapporteur to submit a Type II variation regarding the persistence of Infanrix hexa.
Nevertheless, MS1 would like to comment that the immune responses in the subjects after a booster dose with Engerix-B children around 14 years after the primary vaccination course were rather low. In previous studies the boosterability of the subjects was higher and one month after the challenge dose, around 100 % reached seroprotective levels anti-HBs antibody concentrations ≥ 10 mIU/ml.