17 December 2015
EMA/303961/2016
Procedure Management and Committees Support Division

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

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/P46/117

Note

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

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Introduction

On 28 September 2015, the MAH submitted the final study report of study **DTPa-HBV-IPV-114** for Infanrix hexa, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

1. Scientific discussion

1.1. Information on the development program

The MAH stated that study 106793 (DTPa-HBV-IPV-114) is a standalone study. The main objective of the study was to determine the **persistence of antibodies against hepatitis B** from childhood to adolescence that was conferred by infant vaccination with Infanrix hexa as part of routine vaccination in Germany: three doses of primary vaccination received by 9 months of age and one booster dose received between 11 and 18 months of age.

In the global context of vaccination against hepatitis B, the EMA has requested GSK Biologicals to set up a **long-term surveillance programme** of vaccines containing a recombinant hepB component.

A long-term surveillance programme was requested because combination of more antigens in a vaccine can result in antigenic “interference”, resulting in a lower immune response than achieved by monovalent vaccines. This has been noted in the past with HBV combination products, therefore this is thoroughly followed for this vaccine (Infanrix hexa).

This study is the third in a series of four studies constituting a common immunological follow-up program in healthy subjects who had received four consecutive doses of Infanrix hexa:

- DTPA-HBV-IPV-112: subjects of **4-5 years of age** (study report of 04 December 2008).
- DTPA-HBV-IPV-113: subjects of **7-8 years of age** (study report of 28 March 2012).
- DTPA-HBV-IPV-114: subjects of **12-13 years of age** (study report of 17 August 2015).
- DTPA-HBV-IPV-115: subjects of **14-15 years of age** (planned study).

1.2. Information on the pharmaceutical formulation used in the study

A single challenge dose of the hepatitis B vaccine (Engerix-B Kinder, Expiry date: 31 January 2015) was given to children who received routine vaccination in the year 2001-2002 with Infanrix hexa and had reached the age of 12 to 13 years by 2014. One dose (0.5 ml) contained **10 mcg HBsAg** (hepatitis B surface antigen) adsorbed on 0.25 mg aluminium as aluminium hydroxide.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final report for:

• Study 106793 (DTPa-HBV-IPV-114), an open-label, phase IV, multicentre study to assess the long-term persistence of antibodies against hepatitis B and the immunogenicity and safety of a single dose hepatitis B (Engerix™-B Kinder) vaccine challenge in adolescents aged 12-13 years (from and including the 12th birthday up to but excluding the 14th birthday), previously primed and boosted in the first two years of life with four doses of GSK Biologicals’ DTPa-HBV-IPV/Hib (Infanrix™ hexa) vaccine.

1.3.2. Clinical study

Study 106793 (DTPa-HBV-IPV-114), an open-label, phase IV, multicentre study to assess the long-term persistence of antibodies against hepatitis B and the immunogenicity and safety of a single dose hepatitis B (Engerix™-B Kinder) vaccine challenge in adolescents aged 12-13 years, previously primed and boosted in the first two years of life with four doses of GSK Biologicals' DTPa-HBV-IPV/Hib (Infanrix™ hexa) vaccine.

Description

This was a phase IV, open-label, non-randomised, multicentre study in Germany with a single group, with all subjects receiving a single challenge dose of HBV vaccine. Two blood samples were collected, one before the administration of the single challenge dose of HBV vaccine and a second sample approximately one month after the single challenge dose of HBV vaccine. Safety data was collected up to 30 days after administration of the study vaccine.

The first subject was enrolled in the study on 18 February 2014 and the last study visit was on 23 September 2014.

Methods

Objectives

Primary objective

Immunogenicity

- The anti-HBs antibody response, in terms of subjects with antibody concentrations ≥ 100 mIU/ml, to a single challenge dose of HBV vaccine (Engerix-B Kinder) in subjects 12–13 years of age, previously vaccinated with four doses of Infanrix hexa in the first two years of life, was assessed.

Secondary objective

Immunogenicity

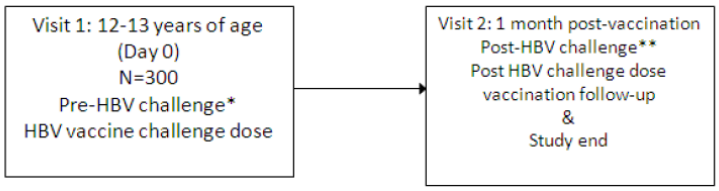
- The persistence of anti-HBs antibodies, in terms of seroprotection status and antibody concentrations, in subjects 12-13 years of age, previously vaccinated with four doses of Infanrix hexa in the first two years of life, was assessed.
- The immunological response to the hepatitis B antigen, in terms of seroprotection status and antibody concentrations, one month after the single challenge dose of the HBV vaccine in subjects 12-13 years of age, previously vaccinated with four doses of Infanrix hexa in the first two years of life, was assessed.

Safety

- The safety and reactogenicity of a single challenge dose of HBV vaccine (Engerix-B Kinder) in terms of solicited symptoms (local and general), unsolicited symptoms and serious adverse events (SAEs), was evaluated.

Study design

Phase IV, open-label, non-randomised, multicentre study in Germany with a single group and all subjects receiving a single challenge dose of HBV vaccine. Collection of blood samples before and one month post HepB challenge dose.



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

Study population

Inclusion criteria

- A male or female between the ages of 12 to 13 (from and including the 12th birthday, up to but excluding the 14th birthday) at the time of enrolment.
- Subjects with documented evidence of previous vaccination with four consecutive doses of Infanrix hexa as part of routine vaccination in Germany: three doses of primary vaccination received by 9 months of age and one booster dose received between 11 and 18 months of age.
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Female subjects of non-childbearing potential could be enrolled in the study. Non-childbearing potential was defined as pre-menarche, current tubal ligation, hysterectomy, ovariectomy or post-menopause.
- Female subjects of childbearing potential might be enrolled in the study, if the subject had practiced adequate contraception for 30 days prior to vaccination, and had a negative pregnancy test on the day of vaccination, and had agreed to continue adequate contraception during the entire treatment period and for 2 months after completion of the vaccination series.

Exclusion criteria

- Child in care
- Administration of long-acting immune-modifying drugs at any time during the study period (e.g. infliximab).
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs within six months prior to the vaccination. [For corticosteroids, this meant prednisone ≥ 0.5 mg/kg/day (for paediatric subjects), or equivalent]. Inhaled and topical steroids were allowed.
- Administration of any chronic drug therapy was to be continued during the study period.
- Planned administration/administration of a vaccine not foreseen by the study protocol during the period starting from 30 days before and ending 30 days after the HBV challenge dose, with

the exception of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (dTpa) vaccine, which could be given as part of routine vaccination practice.

- Concurrent participation in another clinical study, at any time during the study period, in which the subject had been or could be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
- 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.
- Hepatitis B vaccination at birth.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Family history of congenital or hereditary immunodeficiency.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Major congenital defects or serious chronic illness including thrombocytopenia and bleeding disorders.
- History of any neurological disorders or seizures.
- Acute disease and/or fever at the time of enrolment. Fever was defined as temperature ≥ 37.5°C for oral, axillary or tympanic route, or ≥ 38.0°C on rectal route. The preferred route for recording temperature in this study was axillary.
- Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever were enrolled at the discretion of the investigator.
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests
- Administration of immunoglobulins and/or any blood products within the 3 months preceding the dose of study vaccine or planned administration during the study period.
- Pregnant or lactating female.
- Female planned to become pregnant or planning to discontinue contraceptive precautions.

Sample size

A total of **300 subjects** were vaccinated and all subjects completed the study and were therefore included in the ATP cohort for safety. Seven subjects were excluded and therefore **293 subjects** were included in the ATP cohort for analysis of immunogenicity and antibody persistence.

The study was adequately powered to lead to a LL of the 95% CI not more than 5% below that true percentage (i.e. a LL above 91% to 93%, respectively). For instance, if the true percentage of response to the HBV vaccine challenge is 97%, a sample size of 270 subjects provided a power of at least 93% for the LL of the 95% 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 92%.

Table 1. Number of subjects enrolled into the study as well as the number of subjects excluded from ATP analyses with reasons for exclusion

	HBV Group		
Title	**n**	**s**	**%**
Total cohort	301		
Study vaccine dose not administrated but subject number allocated (code 1030)	1	1	
Total vaccinated cohort	300		100
ATP cohort for safety	300		100
Protocol violation (inclusion/exclusion criteria) (code 2010)	2	2	
Concomitant infection related to the vaccine which may influence immune response (code 2060)	3	3	
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	1	1	
Essential serological data missing (code 2100)	1	1	
ATP cohort for analysis of immunogenicity	293		97.7
Protocol violation linked to the inclusion /exclusion criteria (code 3010)	2	2	
Subjects with evidence of hepatitis b infection or disease (including anti-HBc at post-HBV challenge dose time point) (code 3020)	3	4	
Subjects for whom serological results are not available at the pre-HBV challenge blood sampling time point (code 3030)	2	2	
ATP cohort for analysis of antibody persistence	293		97.7

HBV Group = Subjects who previously received *Infanrix hexa* and received a challenge dose of HBV vaccine in this study
Note: Subjects may have more than one elimination code assigned therefore for each elimination reason n (s) is provided
Where:
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort

Treatments

One single dose of HepB vaccine was administered in this study. A blood sample was collected from all subjects at Visit 1 of this study before the challenge dose and again at Visit 2, about one mont post challenge dose.

Endpoints

Primary endpoint

Immunogenicity

- **Anti-HBs immune response to a single challenge dose**: Anti-HBs antibody concentrations **≥ 100 mIU/ml**, one month after the single challenge dose of HBV vaccine.

Secondary endpoint

Immunogenicity

- **Anti-HBs antibody persistence at 12-13 years of age**, after previous vaccination with Infanrix hexa: Anti-HBs antibody concentrations ≥ 6.2 mIU/ml, ≥ 10 mIU/ml, 10 to < 100 mIU/ml, ≥ 100 mIU/ml and anti-HBs antibody concentrations before the single challenge dose of HBV vaccine.
- **Anti-HBs immune response**:
    - Anti-HBs antibody concentrations ≥ 6.2 mIU/ml, ≥ 10 mIU/ml and anti-HBs antibody concentrations one month after the single challenge dose of HBV vaccine.
    - Anamnestic response to the single challenge dose of HBV vaccine, defined as: ≥ 4-fold rise in post-vaccination anti-HBs antibody concentrations in subjects seropositive at the pre-vaccination time point; or post-vaccination, anti-HBs antibody concentrations ≥ 10 mIU/ml in subjects seronegative at the pre-vaccination time point.

Safety

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

Statistical Methods

ATP cohort for analysis of safety

All vaccinated subjects:

- who have received the challenge dose of study vaccine
- for whom administration site of study vaccine was known and was according to protocol and
- who have not received a vaccine not specified or forbidden in the protocol.

ATP cohort for analysis of immunogenicity

All subjects from the ATP cohort for analysis of safety:

- who met all eligibility criteria
- who complied with the procedures and intervals defined in the protocol
- who did not meet any of the elimination criteria during the study
- for whom post-vaccination immunogenicity (Visit 2) results were available.

The interval between vaccination at Visit 1 and blood sampling at Visit 2, considered for inclusion of a subject in the ATP cohort for analysis of immunogenicity, was 21-48 days.

ATP cohort for analysis of antibody persistence

All enrolled subjects:

- aged 12–13 years (from and including the 12th birthday up to but excluding the 14th birthday) at the time of enrolment.
- who had not received any additional dose of hepatitis B vaccine (or any other vaccine with this antigen component) other than the four doses of Infanrix hexa during the first two years of life.
- with no evidence of hepatitis B infection or disease (including anti-HBc at post-HBV challenge dose time point).
- for whom serological results were available at the pre-HBV challenge blood sampling time point.

Derived and transformed data

- A **seronegative subject** was a subject with anti-HBs antibody concentration below the assay cut-off (< 6.2 mIU/ml).

- A **seropositive subject** was a subject with anti-HBs antibody concentrations above the assay cut-off (≥ 6.2 mIU/ml).
- A **seroprotected subject** was a subject with anti-HBs antibody concentrations above the protection level ≥ 10 mIU/ml.
- Anamnestic response to the single challenge dose was defined as:
    - At least (i.e. greater than or equal to) 4-fold rise in post-vaccination anti-HBs antibody concentrations in subjects seropositive at the pre-vaccination time point.
    - Post-vaccination, anti-HBs antibody concentrations ≥ 10 mIU/ml in subjects seronegative at the pre-vaccination time point.
- The Geometric Mean antibody concentration (GMC) calculations were performed by taking the anti-log of the mean of the log10 concentration transformations. All subjects were considered. Subjects whose antibody concentrations were below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMC calculation.
- For a given subject and a given immunogenicity measurement, missing or nonevaluable measurements were not be replaced. Therefore, an analysis excluded subjects with missing or non-evaluable measurements.

Results

Efficacy results

- *Anti-HBs antibody response after the challenge dose (ATP cohort for immunogenicity)*

Table 2. Anti-HBs seropositivity rates, percentage of subjects with antibody concentrations greater than or equal to 10 mIU per ml, greater than or equal to 100 mIU per ml and GMCs (calculated on all subjects) at the post challenge dose time point stratified based on the pre-challenge dose status (ATP cohort for analysis of immunogenicity)

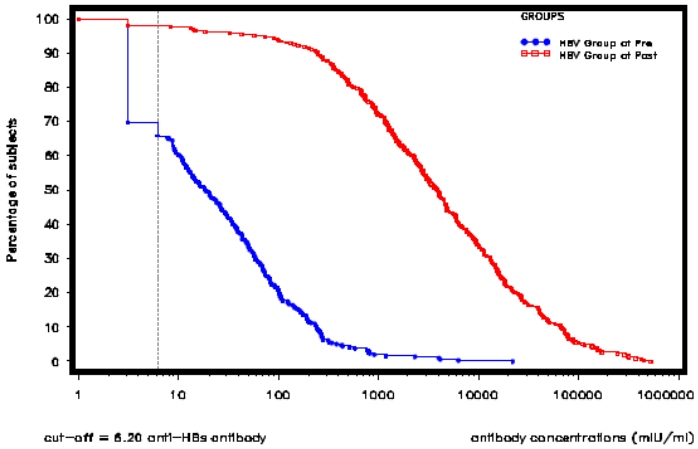
			S+					≥ 10 mIU/ml				≥ 100 mIU/ml				GMC		
						95% CI				95% CI				95% CI			95% CI	
Group	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	value	LL	UL
HBV Group	< 6.2 mIU/ml	Pre	88	0	0.0	0.0	4.1	0	0.0	0.0	4.1	0	0.0	0.0	4.1	3.1	3.1	3.1
		Post	89	83	93.3	85.9	97.5	82	92.1	84.5	96.8	73	82.0	72.5	89.4	476.1	300.0	755.6
	≥6.2 mIU/ml to < 10 mIU/ml	Pre	27	27	100	87.2	100	0	0.0	0.0	12.8	0	0.0	0.0	12.8	7.7	7.1	8.3
		Post	26	26	100	86.8	100	26	100	86.8	100	25	96.2	80.4	99.9	1739.8	944.8	3203.8
	<10 mIU/ml	Pre	115	27	23.5	16.1	32.3	0	0.0	0.0	3.2	0	0.0	0.0	3.2	3.8	3.6	4.1
		Post	115	109	94.8	89.0	98.1	108	93.9	87.9	97.5	98	85.2	77.4	91.1	638.2	431.1	944.7
	≥10 mIU/ml	Pre	176	176	100	97.9	100	176	100	97.9	100	61	34.7	27.7	42.2	70.9	58.0	86.7
		Post	174	174	100	97.9	100	174	100	97.9	100	174	100	97.9	100	10792.2	8354.3	13941.6
	Overall	Pre	291	203	69.8	64.1	75.0	176	60.5	54.6	66.1	61	21.0	16.4	26.1	22.4	18.2	27.5
		Post	289	283	97.9	95.5	99.2	282	97.6	95.1	99.0	272	94.1	90.7	96.5	3502.6	2672.0	4591.5

HBV Group = Subjects who previously received *Infanrix hexa* 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
S+=Seropositive for anti-HBs antibodies (concentrations above the assay cut-off 6.2 mIU/ml)
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre=Blood sampling at pre-challenge dose time point
Post=Blood sampling one month after the challenge dose
Stratification based in pre-challenge dose status:
<6.2 mIU/ml = subjects with antibody concentration <6.2 mIU/ml (Seronegative)
≥6.2-10 mIU/ml = subjects with antibody concentration between 6.2 mIU/ml to 10 mIU/ml
<10 mIU/ml = subjects with antibody concentration <10 mIU/ml
>=10 mIU/ml = subjects with antibody concentration >=10 mIU/ml

One month after the challenge dose of HBV vaccine

- More than 90% of subjects had a **sufficient booster response** (anti-HBs antibody concentrations ≥ 100 mIU/ml): 94.1% [90.7; 96.5]
- More than 95% of subjects were **seroprotected** (antibody concentrations ≥ 10mIU/ml): 97.6% [95.1;99]
- The anti-HBs GMC mounted to 3502.6 mIU/ml [2672; 4591.5].

Figure 1. Reverse cumulative distribution curve of anti-HBs antibody concentration at pre-challenge dose time point and one month after the challenge dose (ATP cohort for analysis of immunogenicity)



HBV Group = Subjects who previously received *Infanrix hexa* and received a challenge dose of HBV vaccine in this study
Pre=Blood sampling at pre-challenge dose time point
Post=Blood sampling one month after the challenge dose

CHMP's comment

The data on anti-HBs antibody response after the challenge dose are obtained from 291 subjects pre-challenge and 289 subjects post-challenge, whereas the ATP cohort for analysis of immunogenicity consisted of 293 subjects. Hence, data were not available from 2 subjects pre-challenge and 4 subjects post-challenge, and this absence of data is not further explained.

- *Antibody persistence*

Table 4. Seropositivity rates, percentage of subjects with greater than or equal to 10 mIU per ml, greater than or equal to 10 mIU per ml to less than 100 mIU per ml, greater than or equal to 100 mIU per ml and GMCs with 95 percent CI for anti-HBs antibody concentrations at pre-challenge dose time point (ATP cohort for analysis of antibody persistence)

			S+				≥ 10 mIU/ml				≥10 mIU/ml to <100 mIU/ml				≥ 100 mIU/ml				GMC		
					95% CI				95% CI				95% CI				95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	value	LL	UL
HBV Group	Pre	293	205	70.0	64.4	75.2	178	60.8	54.9	66.4	116	39.6	34.0	45.4	62	21.2	16.6	26.3	22.7	18.5	27.9

HBV Group = Subjects who previously received *Infanrix hexa* 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
S+=Seropositive for anti-HBs antibodies (concentrations above the assay cut-off 6.2 mIU/ml)
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre=Blood sampling at pre-challenge dose time point

Before the challenge dose of HBV vaccine

- About 60% of subjects were **seroprotected** (persisting seroprotective anti-HBs antibody concentrations of ≥ 10mIU/ml):60.8% [54.9; 66.4].

• *Anamnestic response*

Table 5. Anamnestic response to the challenge dose for anti-HBs antibodies one month after the challenge dose (ATP cohort for analysis of immunogenicity)

			Anamnestic response to the challenge dose			
					95% CI	
Group	Pre-vaccination status	N	n	%	LL	UL
HBV Group	S-	87	80	92.0	84.1	96.7
	S+	200	197	98.5	95.7	99.7
	Total	287	277	96.5	93.7	98.3

HBV Group = Subjects who previously received *Infanrix hexa* and received a challenge dose of HBV vaccine in this study
S-=Seronegative subjects (antibody concentration <6.2 mIU/ml for anti-HBs) prior to vaccination
S+=Seronegative subjects (antibody concentration ≥6.2 mIU/ml for anti-HBs) prior to vaccination
Total=Subjects either seropositive or seronegative at pre-vaccination
Challenge dose response is defined as:
For initially seronegative subjects antibody concentration greater than or equal to 10mIU/ml
For initially seropositive subjects antibody concentration at least four times the pre-challenge antibody concentration
N=Number of subjects with both pre- and post vaccination results available
n/%=number/percentage of responders
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

The anamnestic response to the hepatitis B challenge dose was mounted by 96.5% of subjects [93.7; 98.3].

CHMP's comment

The generated immunogenicity data are consistent with previous data on Engerix-B Junior as a booster vaccine.

Safety results

• *Solicited local and general symptoms*

Pain at the injection site was the most frequent solicited local symptom (44.0%). The most frequent Grade 3 solicited local symptom reported was swelling at the injection site (0.7%).

Table 6. Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort).

		HBV Group				
					95 % CI	
Symptom	Type	N	n	%	LL	UL
Fatigue	All	300	73	24.3	19.6	29.6
	Grade 2 or 3	300	27	9.0	6.0	12.8
	Grade 3	300	6	2.0	0.7	4.3
	Related	300	41	13.7	10.0	18.1
	Grade 3 Related	300	6	2.0	0.7	4.3
	Medical advice	300	0	0.0	0.0	1.2
Gastrointestinal symptoms	All	300	34	11.3	8.0	15.5
	Grade 2 or 3	300	11	3.7	1.8	6.5
	Grade 3	300	4	1.3	0.4	3.4
	Related	300	14	4.7	2.6	7.7
	Grade 3 Related	300	2	0.7	0.1	2.4
	Medical advice	300	0	0.0	0.0	1.2
Headache	All	300	71	23.7	19.0	28.9
	Grade 2 or 3	300	23	7.7	4.9	11.3
	Grade 3	300	7	2.3	0.9	4.7
	Related	300	40	13.3	9.7	17.7
	Grade 3 Related	300	5	1.7	0.5	3.8
	Medical advice	300	0	0.0	0.0	1.2
Temperature/(Axillary) (°C)	All	300	7	2.3	0.9	4.7
	≥37.5	300	7	2.3	0.9	4.7
	>38.0	300	1	0.3	0.0	1.8
	>38.5	300	1	0.3	0.0	1.8
	>39.0	300	0	0.0	0.0	1.2
	Related	300	4	1.3	0.4	3.4
	>39.0 Related	300	0	0.0	0.0	1.2
	Medical advice	300	0	0.0	0.0	1.2

HBV Group = Subjects who previously received *Infanrix hexa* and received a challenge dose of HBV vaccine in this study
N = number of subjects with the documented dose
n/% = number/percentage of subjects reporting the symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
Grade 2 for Headache: Headache that interferes with normal activity
Grade 2 for Temperature :> 38.0 ºC and ≤39.0 ºC
Grade 2 for Fatigue: Fatigue that interferes with normal activity
Grade 2 for Gastrointestinal symptoms: Gastrointestinal symptoms that interfere with normal activity
Grade 3 For Headache: Headache that prevents normal activity
Grade 3 for Temperature: > 39.0ºC
Grade 3 for Fatigue: Fatigue that prevents normal activity
Grade 3 for Gastrointestinal symptoms: Gastrointestinal symptoms that prevent normal activity
Grade 2 or 3= Subjects who reported either grade2 or grade 3 symptoms

Fatigue and headache were the most frequent solicited general symptom (24.3% and 23.7%, resp.). Fever occurred in 7 out of 300 subjects, with one subject reporting temperature >38° C and one subject reporting temperature >38.5° C.

- *Unsolicited Adverse Events (AEs)*

During the 31-day (Days 0-30) post-vaccination period:

- At least one unsolicited symptom was reported for 14.7% of subjects.
- The most frequently reported unsolicited symptom was upper respiratory tract infection, which was reported for 3.3% of the subjects.
- The following unsolicited symptoms of Grade 3 intensity were reported for 0.3% of subject each: abdominal pain, pyrexia, gastrointestinal infection, contusion, headache and cough.
- The following unsolicited symptoms, reported for 0.3% of subject each, were considered by the investigator to be causally related to vaccination: vertigo and urticaria. These adverse events are already mentioned in the SmPC of Engerix-B Junior.

- *SAEs*

No fatal events were reported in this study.

Two SAEs were reported during the study, which were not considered by the investigator to be causally related to the vaccination: contusion of lumbar spine and fracture of right forearm.

CHMP's comment

The generated safety data are consistent with previous data on Engerix-B Junior as a booster vaccine.

1.3.3. Discussion on clinical aspects

The current study investigated the HepB antibody persistence in 300 healthy 12 to 13-year-old adolescents who were previously vaccinated during infancy with 3 doses in their 1th year of life and a fourth dose in their 2nd year of life Infanrix hexa.

One month after the challenge dose of HBV vaccine, more than 90% of subjects (94.1% [90.7; 96.5]) had a booster response ≥ 100 mIU/ml and more than 95% of subjects (97.6% [95.1;99]) were seroprotected, while 96.5% [93.7; 98.3] of subjects mounted an anamnestic response.

Before the challenge dose of HBV vaccine, about 60% of subjects (60.8% [54.9; 66.4]) were still seroprotected at the age of 12 to 13 years.

For long-term protection against HBV, the boosterability (indicating immune memory) is more important than the persistence of antibodies. The study showed good boosterability which indicates long-term protection up to the age of 12-13.

The challenge dose of HBV vaccine was generally well tolerated.

Pain at the injection site was the most frequent solicited local symptom (44.0%) and the most frequent Grade 3 solicited local symptom reported was swelling at the injection site (0.7%). Fatigue and headache were the most frequent solicited general symptom (24.3% and 23.7%, resp.). Fever occurred in 7 out of 300 subjects, with one subject reporting temperature >38° C and one subject reporting temperature >38.5° C. Unsolicited symptoms were reported for 14.7% of the subjects during the 31-day follow-up period.

Two SAEs were reported during the study, which were not considered by the investigator to be causally related to the vaccination: contusion of lumbar spine and fracture of right forearm.

No fatal events were reported in this study.

2. CHMP's overall conclusion and recommendation

Overall conclusion

The article 46 paediatric submission is considered fulfilled, and no further regulatory action is needed. The provided data do not cause concern regarding efficacy or safety of Infanrix hexa.

The benefit/risk balance of Infanrix hexa therefore remains positive.

Recommendation

☒ **Fulfilled:**

No regulatory action required.

Additional clarifications requested

Not applicable.

MS comments:

The conclusions of the Rapporteur are endorsed. In addition, in order to put this study in a clinical perspective it is suggested to add in the AR that a long-term surveillance programme was requested because combination of more antigens in a vaccine can result in antigenic “interference”, resulting in a lower immune response than achieved by monovalent vaccines. This has been noted in the past with HBV combination products, therefor this is thoroughly followed for this vaccine (Infanrix hexa). Furthermore it is recommended to mention that for long-term protection against HBV, the boosterability (indicating immune memory) is more import than the persistence of antibodies. The study showed good boosterability which indicates that there is a long-term protection up to the age of 12-13.

Response to MS comment:

The MS comment is endorsed and the suggestions have been added to the AR for additional clarity.