27 June 2013
EMA/355023/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report under Article 46

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/P46/099.1

Note

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

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1. ADMINISTRATIVE INFORMATION

1.1. Executive Summary

A total of 9 studies evaluating the commercial formulation of Infanrix Hexa are included in the current report. Of these, four studies evaluated safety and immunogenicity of the Infanrix Hexa vaccine in primary immunization studies (116, 106, 100 and 109) or booster vaccination studies (120 and 117). Studies 120 and 117 are the booster studies of primary studies 116 and 109, respectively. Three studies, 110, 111 and 112, are antibody persistence studies. Reactogenicity and immunogenicity data of the primary and booster studies are not different from those reported in initial studies. Results of the antibody persistence studies show that persisting antibodies were present in 4 to 9 year old children vaccinated during infancy with 4 doses of Infanrix Hexa and these data are in line with what was reported in previous studies.

No SmPC and PL changes are proposed.

1.2. Recommendation

No further action required.

2. INTRODUCTION

On 27/12/2012, the MAH submitted completed paediatric studies for Infanrix Hexa, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Infanrix Hexa and that there is no consequential regulatory action.

It is to be noted that the synopses of these studies had already been submitted to the Agency, as part of a renewal procedure submitted in March 2010, for which the Commission Decision was issued on August 30th 2010. The studies have also been submitted in form of a line listing with cover letter as part of an Article 46 submission on March 26, 2010, for which the Assessment Report was issued on June 22nd 2010.

The applicant (GSK Biologicals) states that, in accordance with Article 16(2) of Regulation (EC) No 726/2004, the data submitted do not influence the benefit-risk balance for the above mentioned product and therefore do not require taking further regulatory action on the marketing authorisation for the above mentioned product, in line with the previous Assessment Report and Commission Decision.

GlaxoSmithKline Biologicals had reviewed the results of these studies and concluded that an update of the SmPC is not considered necessary.

3. SCIENTIFIC DISCUSSION

Clinical aspects

3.1. Introduction

The MAH submitted final reports for:

- DTPa-HBV-IPV-116: A phase II, observer-blind, randomized study to evaluate the immunogenicity, safety and reactogenicity of GlaxoSmithKline (GSK) Biologicals' another formulation of DTPa-HBV-IPV/Hib, compared to the currently licensed GSK Biologicals' DTPa-HBV-IPV/Hib vaccine (Infanrix hexa) when administered to healthy infants at 2, 3 and 4 months of age.
- DTPa-HBV-IPV-120: A phase II open, study to assess the immunogenicity and reactogenicity of GlaxoSmithKline (GSK) Biologicals' combined DTPa-HBV-IPV/Hib vaccine when administered as a booster dose to children aged 16-20 months, previously primed with GSK Biologicals' another formulation of DTPa-HBV-IPV/Hib, or with GSK Biologicals' licensed DTPa-HBV-IPV/Hib vaccine (Infanrix hexa) in the primary vaccination study DTPa-HBV-IPV-116.
- DTPa-HBV-IPV-100: An open, multicentre, post-marketing surveillance (PMS) study to assess the safety and reactogenicity of GlaxoSmithKline Biologicals' DTPa-IPV/Hib vaccine administered at 3 and 4 months of age and DTPa-HBV-IPV/Hib vaccine (Infanrix hexa) administered at 5 months of age, as primary vaccination course, followed by administration of GSK Biologicals' DTPa-IPV/Hib vaccine at 18 months of age in healthy infants who received hepatitis B vaccine at birth and at one month of age.
- DTPa-HBV-IPV-106: A phase IIIb, open, randomised, multicentre study to evaluate the immunogenicity and safety of GlaxoSmithKline Biologicals' combined diphtheria-tetanus-acellular pertussis-hepatitis B inactivated polio-conjugated *Haemophilus influenzae* type b vaccine (Infanrix hexa) in Indian infants according to a 6-10-14 week schedule, when compared to Infanrix hexa given to Indian infants according to a 2-4-6 month schedule.
- DTPa-HBV-IPV-109: A phase III, partially double-blind clinical trial to evaluate the immunogenicity and reactogenicity of GlaxoSmithKline (GSK) Biologicals' combined DTPa-HBV-IPV/Hib vaccine (new formulation) as compared with GSK Biologicals' combined DTPa-HBV-IPV/Hib vaccine (current formulation) administered in healthy infants at 3, 4 and 5 months of age. The immunogenicity, safety and reactogenicity of the DTPa-HBV-IPV vaccine was also evaluated in a third group of subjects.
- DTPa-HBV-IPV-117: A phase IV, partially double-blind, multicentre study to assess the immunogenicity and reactogenicity of GlaxoSmithKline (GSK) Biologicals' combined DTPa-HBV-IPV/Hib vaccine (new formulation) as compared with GSK Biologicals' combined DTPa-HBV-IPV/Hib vaccine (current formulation) when administered as a booster dose to children aged 18-23 months, previously primed with the same vaccines in the primary vaccination study DTPa-HBV-IPV-109 (105910). The immunogenicity and reactogenicity of a booster dose of the DTPa-HBV-IPV vaccine was evaluated in a third group of subjects who had received this vaccine in the primary study.

- DTPa-HBV-IPV-110: 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 vaccine challenge in healthy children 7 to 9 years old, previously vaccinated with 4 doses of GlaxoSmithKline (GSK) Biologicals' DTPa-HBV-IPV/Hib vaccine or 4 doses of GSK Biologicals' HBV vaccine, in clinical trials conducted by GSK Biologicals.
- DTPa-HBV-IPV-111: 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 vaccine challenge in healthy children 4-6 years old, previously vaccinated with 4 doses of GlaxoSmithKline (GSK) Biologicals' DTPa-HBV-IPV/Hib vaccine, in clinical trials conducted by GSK Biologicals.
- DTPa-HBV-IPV-112: An open, phase IV, single-group multicentre study to assess the long-term persistence of antibodies against hepatitis B and the immune response to a hepatitis B vaccine challenge in children at 4-5 years of age, previously primed and boosted in the first two years of life with GSK Biologicals' DTPa-HBV-IPV/Hib vaccine.

3.2. Clinical studies

DTPa-HBV-IPV-116

- **Primary objective:** To demonstrate that the immunogenicity of another formulation of DTPa-HBV-IPV/Hib vaccine (preservative-free formulation) in terms of antibody response to all vaccine antigens is non-inferior to that of the DTPa-HBV-IPV/Hib vaccine (licensed formulation), one month after a three-dose primary vaccination course.
- **Conclusions:** The primary and secondary study objectives of non-inferiority of another formulation of DTPa-HBV-IPV/Hib (preservative-free and preservative-containing formulation) to DTPa-HBV-IPV/Hib were not met.
- In the two groups receiving another formulation of DTPa-HBV-IPV/Hib vaccine, at least 92.6% of the subjects were seroprotected against diphtheria, tetanus, hepatitis B, poliovirus types 1 and 3 and Hib antigens. Seroprotection rates of 74% to 80% were observed against poliovirus type 2 in the three groups. Vaccine response was seen in at least 89.6% of the subjects against pertussis antigens.
- The exploratory comparison of groups showed significantly lower antibody GMCs or GMTs for all vaccine antigens, except for poliovirus type 2, after vaccination with the two another formulations of DTPa-HBV-IPV/Hib as compared to the DTPa-HBV-IPV/Hib vaccine.
- The two another formulations of DTPa-HBV-IPV/Hib were well tolerated, with similar incidences of solicited symptoms observed after the DTPa-HBV-IPV/Hib vaccine. Fever > 39.5°C (rectal temperature) was observed for less than 1% of the subjects.
- None of the SAEs reported during the study was considered by the investigator to be causally related to vaccination and all events had resolved at the time of last contact.

Tables 3 and 4 present the assessment of the primary objective.

Synopsis Table 3: Difference in the seroprotection rates between Control and PF Group one month after third vaccine dose for the ATP cohort for immunogenicity.

		PF Group		Control Group		Difference in seroprotection rate (Control Group minus PF Group)		
						Difference	95 % CI	
Antibody	Cut-off	N	%	N	%		LL	UL
Anti-diphtheria (Vero)	0.016 IU/ml	138	97.8	145	100	2.17	-0.44	6.20*
Anti-diphtheria (ELISA)	0.1 IU/ml	138	98.6	146	100	1.45	-1.13	5.13*
Anti-tetanus	0.1 IU/ml	138	100	146	100	0.00	-2.56	2.71*
Anti-HBs	10 mIU/ml	135	92.6	143	98.6	6.01	1.42	11.87
Anti-PRP	0.15 µg/ml	138	95.7	145	95.2	-0.48	-5.86	4.94*
Anti-poliovirus type 1	8ED50	128	93.0	121	96.7	3.73	-2.06	9.97*
Anti-poliovirus type 2	8ED50	121	74.4	130	76.2	1.77	-8.89	12.52
Anti-poliovirus type 3	8ED50	131	96.2	128	97.7	1.47	-3.32	6.59*

* UL below the pre-defined limit for non-inferiority of 10% for seroprotection rates
PF Group received the [redacted] formulation [redacted] at 2, 3 and 4 months of age and Control Group received licensed formulation of DTPa-HBV-IPV/Hib at 2, 3 and 4 months of age
N = number of subjects with available results for seroprotection rates; % = percentage of subjects with anti-<each antibody> concentration ≥ cut-off; 95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Synopsis Table 4: Anti-pertussis GMC ratios between Control and PF Groups one month after third vaccine dose for the ATP cohort for immunogenicity.

Antibody	Group	N	Adjusted GMC	Group	N	Adjusted GMC	Ratio order	Value	95% CI	
Anti-PT	Control	142	68.2	PF	134	59.2	Control Group /PF Group	1.15	1.02	1.29*
Anti-FHA	Control	140	199.3	PF	133	136.9	Control Group /PF Group	1.46	1.28	1.67
Anti-PRN	Control	142	117.3	PF	134	70.8	Control Group /PF Group	1.66	1.40	1.95

* UL below the pre-defined limit for non-inferiority of 1.5 for GMC ratios
PF Group received the [redacted] formulation [redacted] at 2, 3 and 4 months of age and Control Group received licensed formulation of DTPa-HBV-IPV/Hib at 2, 3 and 4 months of age
Adjusted GMC = geometric mean antibody concentration adjusted for baseline concentration
N = Number of subjects with both pre- and post-vaccination results available; 95% CI = 95% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for baseline concentration - pooled variance) LL = lower limit, UL = upper limit

One month after the third dose,

• The upper limits of the standardized asymptotic 95% CIs on the differences between the groups (Control Group minus PF Group) in terms of seroprotection rates against diphtheria (ELISA and Vero), tetanus, poliovirus types 1 and 3 and PRP were below the pre-defined limit of 10%.

• The upper limit of the 95% CI of the group ratio (Control Group divided by PF Group) of anti-PT GMCs was below the pre-defined limit of 1.5.

The upper limits of the standardized asymptotic 95% CIs on the differences between the groups (Control Group minus PF Group) in terms of seroprotection rates against HBs and poliovirus type 2 were above the pre-defined limit of 10% and the upper limits of the 95% CIs of the group ratios (Control Group divided by PF Group) of anti-FHA and anti-PRN GMCs were above the pre-defined limit of 1.5.

Hence the PF formulation was not demonstrated to be non-inferior to the licensed formulation. Similarly, the secondary objective of non-inferiority of the PC formulation to the licensed formulation was not met as the upper limit of the 95% CI for the group differences in seroprotection rates against poliovirus virus type 1 exceeded the pre-defined limit of 10%, and the upper limit of the 95% CI for the ratio of anti-PT, FHA and PRN GMCs exceeded the pre-defined limit of 1.5.

The feasibility of the [redacted] formulations was not demonstrated and they will not be further developed as such by the Company.

DTPa-HBV-IPV-120

- **Co-primary objectives:** To assess the immunogenicity of another formulation of DTPa-HBV-IPV/Hib (preservative-free or preservative-containing), in terms of persistence of the antibodies to all vaccine antigens at the time of the booster vaccination.
- To assess the immunogenicity of a booster dose of DTPa-HBV-IPV/Hib vaccine given after primary vaccination with another formulation of DTPa-HBV-IPV/Hib (preservative-free or preservative-containing), in terms of response to all vaccine antigens.
- **Conclusions (Table 1):** The antibody persistence at the pre-booster time point was in line with the results of the primary vaccination study.
- One month after booster vaccination with the licensed formulation of Infanrix hexa, strong immune responses to all vaccine antigens were elicited in all three study groups and a marked increase in GMCs for antibodies against each vaccine component was observed.
- The Infanrix hexa booster dose was well tolerated. Four SAEs were reported during the study, none of which were considered causally related to vaccination by the investigator. No fatal SAEs were reported in the course of the study.
- The reactogenicity and safety of Infanrix hexa in this study are in agreement with the documented safety profile of the vaccine.

Table 1: The seroprotection rates, seropositivity rates and GMCs of antibodies to all vaccine antigens, before and one month after the booster vaccination (ATP cohort for immunogenicity).

Antibody	Group	Time point	N	n	SP/S+%	95% CI		GMC*		
						LL	UL	Value	95% CI	
									LL	UL
Anti-diphtheria (≥ 0.1 IU/ml by ELISA or ≥ 0.016 IU/ml by Vero cell assay)	PF	Pre	112	62	64.3	54.7	73.1	0.064	0.058	0.071
		PI (MI)	113	113	100	96.8	100	2.237	1.877	2.666
	PC	Pre	117	77	64.1	54.7	72.8	0.069	0.062	0.076
		PI (MI)	119	118	99.2	95.4	100	2.242	1.868	2.689
	Control	Pre	111	67	75.0	66.5	82.7	0.084	0.073	0.097
		PI (MI)	119	119	100	96.9	100	3.952	3.365	4.642

Antibody	Group	Time point	N	n	SP/S* %	95% CI		GMC/T		
						LL	UL	Value	95% CI	
									LL	UL
Anti-tetanus (≥ 0.1 IU/ml)	PF	Pre	112	93	83.0	74.8	89.5	0.216	0.184	0.254
		PI (MI)	113	113	100	96.8	100	9.799	8.390	11.444
	PC	Pre	117	103	88.0	80.7	93.3	0.248	0.213	0.289
		PI (MI)	119	118	99.2	95.4	100	9.136	7.838	10.648
	Control	Pre	111	95	85.6	77.6	91.5	0.261	0.219	0.310
		PI (MI)	119	119	100	96.9	100	10.833	9.505	12.347
Anti-PT (≥ 5 EL.U/ml)	PF	Pre	109	80	73.4	64.1	81.4	7.6	6.7	9.1
		PI (MI)	111	111	100	96.7	100	150.9	132.9	171.2
	PC	Pre	112	81	72.3	63.1	80.4	7.0	6.1	8.1
		PI (MI)	119	118	99.2	95.4	100	117.1	101.5	135.0
	Control	Pre	110	93	84.5	76.4	90.7	8.9	7.7	10.3
		PI (MI)	119	119	100	96.9	100	153.7	135.1	174.9
Anti-FHA (≥ 5 EL.U/ml)	PF	Pre	110	106	96.4	91.0	99.0	21.7	18.1	25.9
		PI (MI)	112	112	100	96.8	100	609.6	534.1	695.7
	PC	Pre	112	107	95.5	89.9	98.5	22.1	18.5	26.2
		PI (MI)	119	118	99.2	95.4	100	533.7	463.0	615.1
	Control	Pre	109	109	100	96.7	100	33.7	27.6	41.1
		PI (MI)	119	119	100	96.9	100	791.9	706.8	884.6
Anti-PRN (≥ 5 EL.U/ml)	PF	Pre	112	81	72.3	63.1	80.4	8.6	7.1	10.3
		PI (MI)	113	113	100	96.8	100	306.5	261.3	364.2
	PC	Pre	117	86	73.5	64.5	81.2	8.7	7.3	10.2
		PI (MI)	118	117	99.2	95.4	100	311.7	260.3	373.2
	Control	Pre	111	99	89.2	81.9	94.3	15.3	12.6	18.5
		PI (MI)	119	119	100	96.9	100	584.1	469.5	650.1
Anti-HBs (≥ 10 mIU/ml)	PF	Pre	111	106	95.5	89.8	98.5	84.3	65.7	108.2
		PI (MI)	111	110	99.1	95.1	100	3291.7	2373.6	4565.0
	PC	Pre	117	112	95.7	90.3	98.6	86.2	67.8	109.6
		PI (MI)	118	117	99.2	95.4	100	3528.1	2546.1	4888.9
	Control	Pre	110	106	96.4	91.0	99.0	139.8	107.2	182.3
		PI (MI)	118	118	100	96.9	100	6132.7	4587.8	8197.9
Anti-poliovirus type 1 (≥ 8 ED 50)	PF	Pre	110	67	60.9	51.1	70.1	12.9	10.3	16.3
		PI (MI)	111	110	99.1	95.1	100	726.3	560.4	941.4
	PC	Pre	117	76	65.0	55.6	73.5	15.2	12.3	18.9
		PI (MI)	117	117	100	96.9	100	942.4	734.1	1209.7
	Control	Pre	109	84	77.1	68.0	84.6	21.8	17.1	27.4
		PI (MI)	113	112	99.1	95.2	100	1288.8	1029.1	1614.0

Antibody	Group	Time point	N	n	SP/S+ %	95% CI		GMC/T		
						LL	UL	Value	95% CI	
									LL	UL
Anti-polio virus type 2 (≥ 8 ED 50)	PF	Pre	111	48	43.2	33.9	53.0	8.1	7.3	11.3
		PI (MI)	112	110	98.2	93.7	99.8	712.8	529.1	960.4
	PC	Pre	117	51	43.6	34.4	53.1	8.7	7.2	10.5
		PI (MI)	117	117	100	96.9	100	812.9	632.8	1044.3
	Control	Pre	109	56	51.4	41.8	61.1	11.8	9.2	15.0
		PI (MI)	113	112	99.1	95.2	100	1231.0	981.0	1576.9
Anti-polio virus type 3 (≥ 8 ED 50)	PF	Pre	111	58	52.3	42.8	61.8	9.5	7.9	11.6
		PI (MI)	112	111	99.1	95.1	100	760.0	591.0	1029.3
	PC	Pre	117	77	65.8	56.5	74.3	16.0	12.6	20.4
		PI (MI)	117	117	100	96.9	100	1145.8	891.6	1472.5
	Control	Pre	109	82	75.2	66.0	83.0	21.3	16.4	27.7
		PI (MI)	113	113	100	96.8	100	1794.8	1426.8	2257.7
Anti-PRP (≥ 0.15 µg/ml)	PF	Pre	111	71	64.0	54.3	72.9	0.249	0.199	0.310
		PI (MI)	112	112	100	96.8	100	36.666	28.610	47.504
	PC	Pre	117	87	74.4	65.5	82.0	0.314	0.252	0.392
		PI (MI)	119	119	100	96.9	100	35.318	27.447	45.445
	Control	Pre	111	92	82.9	74.6	89.4	0.487	0.383	0.620
		PI (MI)	119	119	100	96.9	100	77.087	60.224	98.672

PF = Subjects who received the [redacted] formulation [redacted] at 2, 3 and 4 months of age and the licensed formulation of DTPa-HBV-IPV/Hib booster dose at 16-20 months of age
PC = Subjects who received the [redacted] formulation [redacted] at 2, 3 and 4 months of age and the licensed formulation of DTPa-HBV-IPV/Hib booster dose at 16-20 months of age
Control = Subjects who received the licensed formulation of DTPa-HBV-IPV/Hib at 2, 3 and 4 months of age and as a booster dose at 16-20 months of age
GMC/Ts = geometric mean antibody concentration/titre, calculated for all subjects
' = GMC values for anti-diphtheria based on ELISA
N = number of subjects with available results
SP = Seroprotection; S+ = Seropositivity
n (%) = number (percentage) of subjects with antibody concentrations/titres above the specified cut-off
95% CI = 95% confidence interval; LL= Lower Limit, UL=Upper Limit
PRE = blood sample taken before the booster dose
PI (M1) = blood sample one month after the booster dose

DTPa-HBV-IPV-100

- **Primary objective:** To assess the safety and reactogenicity of the DTPa-HBV-IPV/Hib vaccine and DTPa-IPV/Hib vaccine.
- **Conclusions (Table 1):** Both the study vaccines were well tolerated and demonstrated a good safety profile.
- Two SAEs (febrile convulsions and exanthema subitum) were reported by one subject after administration of the booster dose that were considered by the investigator to have causal relationship to the study vaccine. Both events were resolved during the course of the study.

Synoptic table 1: Incidence of symptoms (per subject) reported during the 4-day (Day 0-3) follow-up period after vaccination (Total Vaccinated cohort)

Symptom	Type	Primary vaccination (N=702)				Booster vaccination (N=688)			
		n	%	LL	UL	n	%	LL	UL
Overall Incidence of nature of symptoms (solicited and unsolicited)									
Any symptom	Any	559	79.6	76.5	82.6	335	48.7	44.9	52.5
	Grade 3 & 4	41	5.8	4.2	7.8	13	1.9	1.0	3.2
General symptoms	Any	521	74.2	70.8	77.4	265	41.4	37.7	45.2
	Grade 3 & 4	29	4.1	2.8	5.9	9	1.3	0.6	2.5
Local symptoms	Any	315	44.9	41.1	48.6	213	31.0	27.5	34.8
	Grade 3 & 4	15	2.1	1.2	3.5	5	0.7	0.2	1.7
		N°=697				N°=565			
Solicited local symptoms									
Pain	Any	227	32.6	29.1	36.2	166	29.4	25.7	33.3
	Grade 3	8	1.1	0.5	2.2	3	0.5	0.1	1.5
Redness (mm)	Any	222	31.9	28.4	35.5	148	26.2	22.6	30.0
	>20 mm	2	0.3	0.0	1.0	2	0.4	0.0	1.3
Swelling (mm)	Any	172	24.7	21.5	28.1	115	20.4	17.1	23.9
	>20 mm	6	0.9	0.3	1.9	1	0.2	0.0	1.0
Solicited general symptoms									
Drowsiness	All	261	37.4	33.8	41.2	89	15.8	12.8	19.0
	Grade 3	6	0.9	0.3	1.9	1	0.2	0.0	1.0
	Related	210	30.1	26.7	33.7	89	15.8	12.8	19.0
	Grade 3* Rel	4	0.6	0.2	1.5	1	0.2	0.0	1.0
Fever (Axillary in °C)	Any (≥ 37.5°C)	252	38.2	32.6	39.8	152	26.9	23.3	30.8
	>38.0°C	64	9.2	7.1	11.6	41	7.3	5.3	9.7
	>38.5°C	24	3.4	2.2	5.1	13	2.3	1.2	3.9
	>39.0°C	10	1.4	0.7	2.6	6	1.1	0.4	2.3
	>39.5°C	5	0.7	0.2	1.7	2	0.4	0.0	1.3
	>40.0°C	0	0.0	-	-	1	0.2	0.0	1.0
	Related	238	34.1	30.6	37.8	149	26.4	22.8	30.2
	>39. 0°C* Rel	9	1.3	0.6	2.4	6	1.1	0.4	2.3
Irritability	All	341	48.9	45.2	52.7	163	28.8	25.1	32.8
	Grade 3	17	2.4	1.4	3.9	2	0.4	0.0	1.3
	Grade 4	2	0.3	0.0	1.0	0	0.0	0.0	0.7
	Related	268	38.5	34.8	42.2	162	28.7	25.0	32.6
	Grade 3* Grade 4* Rel	12	1.7	0.9	3.0	2	0.4	0.0	1.3
Loss of appetite	All	276	39.6	35.9	43.3	118	20.9	17.6	24.5
	Grade 3	1	0.1	0.0	0.8	1	0.2	0.0	1.0
	Related	211	30.3	26.9	33.8	117	20.7	17.4	24.3
	Grade 3* Rel	0	0.0	0.0	0.5	1	0.2	0.0	1.0

Study Group = Subjects received DTPa-IPV/Hib at 3, 4 months of age; DTPa-HBV-IPV/Hib at 5 months of age + DTPa-IPV/Hib at 18 months of age.
N= number of subjects with at least one administered dose
N*= number of subjects with at least one documented dose
n (%): Number (percentage) of subjects reporting a specified symptom
Any: Any solicited symptom (irrespective of intensity grade or relationship to vaccination)
Grade 3 pain: Cried when limb was moved/ spontaneously painful; Grade 3 redness/swelling: surface diameter at the injection site >20 mm; Grade 3 drowsiness: Drowsiness that prevented normal activity; Grade 3 irritability: Crying that could not be comforted/ prevented normal activity; Grade 4 irritability: Continuous and unaltered crying for ≥ 3 hours; Grade 3 loss of appetite: Did not eat at all
Related = symptoms considered by the investigator to have causal relationship to vaccination
Grade 3* Rel= Reports of the specified of grade 3 intensity and with a causal relationship to vaccination
Grade 3*Grade4* Rel= Reports of the specified of grade 3 or grade 4 intensity and with a causal relationship to vaccination
95% CI = Exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

DTPa-HBV-IPV-106

- **Primary objective:** To assess the antibody response to pertussis toxoid (PT), filamentous haemagglutinin (FHA), pertactin (PRN) and poliovirus types 1, 2, 3 after a three-dose primary vaccination course with Infanrix hexa.
- **Conclusions (Table 1):** The immunogenicity objectives were not assessed in this study due to a bacterial contamination of the samples prior to shipment for analysis. The Infanrix hexa vaccine was safe and well tolerated when administered to Indian infants according to either a 6-10-14 week or a 2-4-6 month schedule.
- SAEs were reported for three subjects each in the 6-10-14 week group and the 2-4-6 month group in this study. None of these was considered by the investigator to have causal relationship to vaccination.

Synopsis table 1: Reactogenicity reported during the 4-day (Day 0-Day 3) post-vaccination period (according to per subject analysis) for the Total Vaccinated Cohort

		6-10-14 week group					2-4-6 month group				
		N	n	%	95% CI (LL, UL)		N	n	%	95% CI (LL, UL)	
Any symptom		112	94	83.9	75.9	90.2	112	88	78.6	69.8	85.8
General symptoms		112	78	69.6	60.2	78.0	112	72	64.3	54.7	73.1
Local symptoms		112	75	67.0	57.4	75.5	112	73	65.2	55.6	73.9
Solicited local Symptoms N* = 111											
Pain	Any	111	66	59.5	49.7	68.7	110	63	57.3	47.5	66.7
	Grade *3*	111	14	12.6	7.1	20.3	110	11	10.0	5.1	17.2
Redness	Any	111	38	34.2	25.5	43.8	110	52	47.3	37.7	57.0
	> 20 mm	111	7	6.3	2.6	12.5	110	12	10.9	5.8	18.3
Swelling	Any	111	47	42.3	33.0	52.1	110	44	40.0	30.8	49.8
	> 20 mm	111	22	19.8	12.8	28.5	110	16	14.5	8.5	22.5
Solicited general Symptoms N* = 110											
Drowsiness	Any	110	26	23.6	16.1	32.7	110	36	32.7	24.1	42.3
	Grade *3*	110	4	3.6	1.0	9.0	110	1	0.9	0.0	5.0
	Related	110	26	23.6	16.1	32.7	110	36	32.7	24.1	42.3
	Grade *3* Related	110	4	3.6	1.0	9.0	110	1	0.9	0.0	5.0
Fever (axillary temperature)	Any	110	51	46.4	36.8	56.1	110	44	40.0	30.8	49.8
	≥ 37.5 °C	110	51	46.4	36.8	56.1	110	43	39.1	29.9	48.9
	> 38.0 °C	110	13	11.8	6.4	19.4	110	21	19.1	12.2	27.7
	> 38.5 °C	110	7	6.4	2.6	12.7	110	11	10.0	5.1	17.2
	> 39.0 °C	110	3	2.7	0.6	7.8	110	5	4.5	1.5	10.3
	> 39.5 °C	110	0	0.0	0.0	3.3	110	2	0.0	0.0	3.3
	Related	110	51	46.4	36.8	56.1	110	43	39.1	29.9	48.9
	> 39.0 °C related	110	3	2.7	0.6	7.8	110	5	4.5	1.5	10.3
Irritability	Any	110	44	40.0	30.8	49.8	110	48	43.6	34.2	53.4
	Grade *3*	110	5	4.5	1.5	10.3	110	1	0.9	0.0	5.0
	Related	110	43	39.1	29.9	48.9	110	48	43.6	34.2	53.4
	Grade *3* Related	110	5	4.5	1.5	10.3	110	1	0.9	0.0	5.0
Loss of appetite	Any	110	19	17.3	10.7	25.7	110	28	25.5	17.6	34.6
	Grade *3*	110	1	0.9	0.0	5.0	110	2	1.8	0.2	6.4
	Related	110	17	15.5	9.3	23.6	110	28	25.5	16.1	32.7
	Grade *3* Related	110	1	0.9	0.0	5.0	110	1	0.9	0.0	5.0

6-10-14 week group received Infanrix hexa at 6, 10 and 14 weeks of age; 2-4-6 month group received Infanrix hexa at 2, 4 and 6 months of age
N =number of subjects with at least one administered dose; N*= number of subjects with documented doses
n(%)= number(percentage) of subjects presenting at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Grade *3* pain: Pain that prevented normal activity; Grade *3* Drowsiness: Drowsiness that prevented normal activity
Grade *3* irritability: Crying that could not be comforted/ prevented normal activity; Grade *3* loss of appetite: Did not eat at all
Related: Symptoms considered by the investigator to have a causal relationship to vaccination
Grade *3* related: Grade 3 symptom considered causally related to the vaccine by the investigator

DTPa-HBV-IPV-109

- **Primary objective:** To demonstrate that the immunogenicity of the DTPa-HBV-IPV/Hib vaccine (new formulation) in terms of response to all vaccine antigens is non-inferior to that of the DTPa-HBV-IPV/Hib vaccine (current formulation), one month after a three-dose primary vaccination course.
- *Criteria for non-inferiority (one month after the third vaccine dose):*
    - For hepatitis B, PRP, diphtheria, tetanus and poliovirus types 1, 2 and 3, the upper limit of the standardized asymptotic 95% CI on the group difference [DTPa-HBV-IPV/Hib (current formulation) minus DTPa-HBV-IPV/Hib (new formulation)] for the percentage of seroprotected subjects is below 10%.
    - For the pertussis antigens (anti-PT, anti-FHA and anti-PRN antibody concentrations), the upper limit of the 95% CI on the GMC ratio [DTPa-HBV-IPV/Hib (current formulation) divided by DTPa-HBV-IPV/Hib (new formulation)] is below 1.5.
- **Conclusions (Table 1):** The primary objective was met. The preservative-free formulation of the DTPa-HBV-IPV/Hib vaccine was shown to be non-inferior to the current formulation of the vaccine in terms of seroprotection against diphtheria, tetanus, hepatitis, poliovirus types 1, 2 & 3 and *Haemophilus influenzae* type b and in terms of antibody GMCs against PT, FHA and PRN.
- Seroprotection rates against diphtheria, tetanus, HBs, poliovirus types 1, 2 and 3 and seropositivity rates against PT, FHA and PRN were ≥ 96.2% in the three groups and seroprotection rates against PRP were ≥ 94.2% with the two DTPa-HBV-IPV/Hib vaccine formulations.
- The three vaccines were well tolerated and the preservative-free formulation did not modify the reactogenicity of the DTPa-HBV-IPV/Hib vaccine. A significantly lower incidence of some general symptoms (drowsiness and fever) was observed after vaccinating with DTPa-HBV-IPV (preservative-free) as compared to DTPa-HBV-IPV/Hib (preservative-free).

Synopsis table 1 presents the difference between the HexaREF Group and the HexaNEW Group in terms of seroprotection rates and GMC ratios, one month after the third dose for the ATP cohort for immunogenicity.

Antibody	HexaNEW Group		HexaREF Group		Difference in seroprotection rate (HexaREF Group minus HexaNEW Group)		
	N	SP%	N	SP%	%	95 % CI	
						LL	UL
Anti-diphtheria (≥ 0.1 IU/ml)	104	97.1	106	96.2	-0.89	-6.80	4.84*
Anti-tetanus (≥ 0.1 IU/ml)	104	99.0	106	100	0.96	-2.55	5.25*
Anti-HBs [(≥ 10 mIU/ml	116	99.1	123	98.4	-0.76	-4.97	3.24*
Anti-poliovirus type 1 (≥ 8 ED50)	60	100.0	66	100	0.00	-5.50	6.02*
Anti-poliovirus type 2 (≥ 8 ED50)	64	100.0	74	100	0.00	-4.93	5.66*
Anti-poliovirus type 3 (≥ 8 ED50)	71	100.0	72	100	0.00	-5.07	5.13*
Anti-PRP (≥ 0.15 µg/ml)	104	94.2	106	96.2	2.00	-4.31	8.74*
	HexaNEW Group		HexaREF Group				
	N	GMC	N	GMC	GMC ratio (HexaREF Group ÷ HexaNEW Group		
						95%CI**	
						LL	UL
Anti-PT	128	75.2	124	71.2	1.06	0.90	1.24*
Anti-FHA	129	215.8	125	178.0	1.21	1.02	1.44*
Anti-PRN	127	146.7	126	138.3	1.06	0.86	1.31*

HexaNEW Group received the new formulation of DTPa-HBV-IPV/Hib at 3, 4 and 5 months of age
HexaREF Group received the current formulation of DTPa-HBV-IPV/Hib at 3, 4 and 5 months of age
Pentа Group received DTPa-HBV-IPV at 3, 4 and 5 months of age
N = number of subjects with available results; SP% = percentage of subjects with antibody concentration above cut-off
GMC = geometric mean antibody concentration adjusted for baseline concentration
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
**95% CI = 95% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for baseline concentration - pooled variance)
*upper limit of the 95%CI below the predefined limit for non-inferiority: 10% for seroprotection rates and 1.5 for GMC ratios

Non-inferiority analysis: One month after the third dose of the primary vaccination course,

- The upper limit of the standardized asymptotic 95% CI on the difference between the groups (HexaREF Group minus HexaNEW Group) in terms of hepatitis B, PRP, diphtheria, tetanus and poliovirus types 1, 2 and 3 seroprotection rates were all below 10%.
- The upper limit of the 95% CI on the anti-PT, anti-FHA and anti-PRN GMC ratio (HexaREF Group ÷ HexaNEW Group) were all below 1.5.

The non-inferiority of the preservative-free formulation of the DTPa-HBV-IPV/Hib vaccine to the preservative-containing formulation of the vaccine was demonstrated.

DTPa-HBV-IPV-117

- **Primary objective:** To demonstrate that the immunogenicity of the DTPa-HBV-IPV/Hib vaccine (new formulation) in terms of response to all vaccine antigens is non-inferior to that of the DTPa-HBV-IPV/Hib vaccine (current formulation), one month after the booster dose.
- *Criteria for non-inferiority (one month after the booster dose):*
- For hepatitis B, polyribosyl-ribitol-phosphate, diphtheria, tetanus and poliovirus types 1, 2 and 3, the upper limit of the standardized asymptotic 95% confidence interval (CI) on the group difference [DTPa-HBV-IPV/Hib (current formulation) minus DTPa-HBV-IPV/Hib (new formulation)] for the percentage of seroprotected subjects is ≤10%.
- For the pertussis antigens: anti-pertussis toxoid, anti-filamentous haemagglutinin and antipertactin antibody concentrations, the upper limit of the 95% CI on the geometric mean concentration (GMC) ratio [DTPa-HBV-IPV/Hib (current formulation) divided by DTPa- HBV-IPV/Hib (new formulation)] is ≤ 1.5.
- **Conclusions (see Table below):** The immunogenicity results of this study must be interpreted with care as the number of subjects included in the ATP cohort for immunogenicity was lower than expected.
- The booster dose of the preservative-free formulation of the DTPa-HBV-IPV/Hib vaccine was non-inferior to the preservative-containing formulation of the vaccine in terms of immunogenicity against all antigens with the exception of PT. Hence, the primary objective was not met. The study sample size and statistical power was much lower than foreseen and therefore limits the ability to conclude on the primary objective.
- Before the administration of the booster dose, similar persisting seroprotective/ seropositive levels of antibodies were observed against all antigens in all the groups.
- Booster vaccination with the preservative-free formulation of the DTPa-HBV-IPV/Hib vaccine elicited a strong response to all vaccine antigens. Similar responses were observed in subjects receiving preservative-containing formulation of the DTPa-HBV-IPV/Hib vaccine and the DTPa-HBV-IPV vaccine.
- The three vaccines were well tolerated; no SAE related to study vaccination was reported.
- The reactogenicity and safety of the preservative-free formulation of DTPa-HBV-IPV/Hib vaccine in this study is in agreement with the documented safety profile of the preservative-containing Infanrix hexa vaccine.

Immunogenicity results: The immunogenicity analysis was performed on the ATP cohort (primary analysis) and on the Total Vaccinated cohort. Tables 1, 2, 3 and 4 present the results for ATP analysis.

Non-inferiority analysis: One month after the booster dose,

- The upper limit of the standardized asymptotic 95% CI on the difference between groups (HexaREF Group minus HexaNEW Group) in terms of diphtheria, tetanus, hepatitis B, PRP and poliovirus types 1, 2 and 3 seroprotection rates were all below 10%.
- The upper limit of the 95% CI on the GMC ratio (HexaREF Group GMC divided by HexaNEW Group GMC) was below 1.5 for anti-FHA and anti-PRN GMCs and not for anti-PT GMCs.

Thus, non-inferiority of the new [redacted] formulation of the DTPa-HBV-IPV/Hib vaccine to the current [redacted] formulation of the vaccine was not demonstrated in terms of immune response to all vaccine antigens. The failure to meet the pre-defined clinical limit of non-inferiority for anti-PT GMC ratio could be attributed to the reduced sample size and power.

Table 1: Difference between the HexaREF Group and the HexaNEW Group in terms of seroprotection rates and GMC ratios, one month after the third dose for the ATP cohort for immunogenicity.

Antibody	HexaNEW Group		HexaREF Group		Difference in seroprotection rate (HexaREF Group minus HexaNEW Group)		
	N	SP%	N	SP%	%	95 % CI	
						LL	UL
Anti-diphtheria (≥ 0.1 IU/ml)	77	98.7	79	98.2	-2.50	-9.48	3.62
Anti-tetanus (≥ 0.1 IU/ml)	77	98.7	79	98.7	0.03	-5.68	5.68
Anti-HBs (≥ 10 mIU/ml)	91	96.7	92	100	3.30	-0.80	9.27
Anti-poliovirus type 1 (≥ 8 ED50)	55	100	51	100	0.00	-7.07	6.59
Anti-poliovirus type 2 (≥ 8 ED50)	55	100	51	100	0.00	-7.07	6.59
Anti-poliovirus type 3 (≥ 8 ED50)	55	100	52	100	0.00	-6.84	6.59
Anti-PRP (≥ 0.15 µg/ml)	76	97.4	79	98.7	1.37	-4.49	8.01
Antibody	**HexaREF Group**		**HexaNEW Group**		**GMC ratio (HexaREF Group / HexaNEW Group**		
	N	GMC	N	GMC	GMC ratio	95% CI	
						LL	UL
Anti-PT	70	84.2	84	65.5	1.29	0.85	1.94
Anti-FHA	69	426.3	86	476.6	0.90	0.60	1.34
Anti-PRN	77	384.1	89	418.1	0.92	0.57	1.47

HexaNEW = Subjects who received the DTPa-HBV-IPV/Hib (new formulation) vaccine in the primary study (105910) and the current study (110478)
HexaREF = Subjects who received the DTPa-HBV-IPV/Hib (current formulation) vaccine in the primary study (105910) and the current study (110478)
N = number of subjects with available results
SP% = percentage of subjects with anti-HBs antibody concentration ≥ 10 mIU/ml, anti-PRP antibody concentration ≥ 0.15 µg/ml, anti-diphtheria and anti-tetanus antibody concentration ≥ 0.1 IU/ml, anti-poliovirus types 1, 2 and 3 antibody titres ≥ 8 ED50
95% CI = 95% Standardised asymptotic confidence interval / 95% confidence interval for the GMC ratio
LL = lower limit, UL = upper limit
GMC = geometric mean antibody concentration

DTPa-HBV-IPV-110

- **Primary objective:** To assess the anti-HB antibody response to a challenge dose of HBV vaccine in subjects aged 7 to 9 years, previously primed and boosted with 4 doses of Infanrix hexa in the first two years of life.
- **Conclusions (see Table below):** In DTPa-HBV-IPV/Hib vaccinees at 8 years of age, on average 6.5 years after the DTPa-HBVIPV/Hib booster dose given in the second year of life, 77.2% of the subjects in the ATP persistence cohort still had anti-HBs concentrations ≥ 10 mIU/ml.
- At that time, over 90% of the DTPa-HBV-IPV/Hib vaccinees (in the ATP persistence cohort) had seroprotective antibody concentrations or titres against diphtheria, tetanus, the three poliovirus types and PRP and more than 89.6% subjects were seropositive for anti-FHA and anti-PRN; 38.2% of subjects were seropositive for anti-PT.
- A strong increase in anti-HB concentrations, of a magnitude similar to the response to the second year booster, was observed after the HBV vaccine challenge, indicative of the presence of immune memory to HBV.

- After the HBV vaccine challenge, 98.9% of the subjects primed with the DTPa-HBV-IPV/Hib vaccine had anti-HB antibody concentrations ≥ 10 mIU/ml and 93.6% had anti-HB antibody concentrations ≥ 100 mIU/ml. An anamnestic response was observed in 98.9% of the subjects.
- The HBV vaccine was well tolerated, grade 3 solicited symptoms were reported for less than 1% of the subjects and no SAEs were reported.

Hepatitis B results (ATP immunogenicity cohort):

In Group 1 (i.e. DTPa-HBV-IPV/Hib Group):

- Prior to administration of the HBV vaccine challenge dose, 78% of subjects had seroprotective concentrations of anti-HBs antibodies and 33.9% had anti-HBs antibody concentrations ≥ 100 mIU/ml.
- A strong response to the HBV vaccine challenge, indicative of the presence of immune memory was observed. One month after the challenge dose, 98.9% of the subjects had anti-HBs antibody concentrations ≥ 10 mIU/ml and 93.6% had concentrations ≥ 100 mIU/ml, with a 110-fold increase in anti-HBs GMCs from pre- to post-challenge time point.
- An anamnestic response to the HBV vaccine challenge was observed in 98.9% of the subjects.

Synopsis table 2: Percentage of subjects with anti-HBs antibody concentrations of at least 3.3 mIU/ml, at least 10 mIU/ml and at least 100 mIU/ml and geometric mean concentrations (GMC) before and one month after the challenge dose (ATP cohort for immunogenicity).

			≥ 3.3 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
Group 1	Pre	196	165	88.7	83.3	92.9	145	78.0	71.3	83.7	63	33.9	27.1	41.2	37.3	28.9	48.2
	Post	197	186	99.5	97.1	100	185	98.9	96.2	99.9	175	93.6	89.1	96.6	4133.5	2967.9	5757.1
Group 2	Pre	9	9	100	66.4	100	7	77.8	40.0	97.2	2	22.2	2.8	60.0	38.5	13.2	111.7
	Post	9	9	100	66.4	100	9	100	66.4	100	9	100	66.4	100	7698.5	1314.4	45089.6
Total	Pre	195	174	89.2	84.0	93.2	152	77.9	71.5	83.6	65	33.3	26.8	40.4	37.4	29.2	47.9
	Post	196	195	99.5	97.2	100	194	99.0	96.4	99.9	184	93.9	89.5	96.8	4253.3	3078.6	5876.2

Group 1= Subjects previously primed and boosted with 4 doses of GSK Biologicals' DTPa-HBV-IPV/Hib vaccine in the first two years of life; Group 2= Subjects previously primed and boosted with 4 doses of GSK Biologicals' hepatitis B vaccine in the first two years of life; Pre= Prior to the administration of challenge dose; Post: One month after the challenge dose
GMC= geometric mean antibody concentration, calculated for all subjects. Antibody concentrations below the cut-off of the assay were given an arbitrary value of one half the cut-off for the purpose of calculating the GMC.
N= number of subjects with available results; n (%)= number (percentage) of subjects with antibody concentrations above the specified cut-off; 95% CI; LL, UL= exact 95% confidence interval; lower and upper limits

DTPa-HBV-IPV-111

- **Primary objective:** To assess the anti-HB antibody response to a challenge dose of HBV vaccine in subjects aged 4-6 years, previously primed and boosted with 4 doses of *Infanrix hexa* in the first two years of life.
- **Conclusions (see Table below):** At 4.6 years of age, on average 3.6 years after the DTPa-HBV-IPV/Hib booster dose given in the second year of life, 86.4% of the subjects in the ATP persistence cohort still had anti-HBs concentrations ≥ 10 mIU/ml.
- At that time, over 90% of the subjects still had seroprotective antibody concentrations or titres against diphtheria, poliovirus types 1, 2 & 3 and PRP and were seropositive for anti-FHA and anti-PRN; 74.7% of the subjects still had seroprotective concentrations of anti-tetanus antibodies and 25.4% were seropositive for anti-PT.
- A strong increase in anti-HBs concentrations, of a higher magnitude than the response to the second year booster, was observed after the HBV vaccine challenge, indicative of the presence of immune memory to HBV.
- After the HBV vaccine challenge, 98.4% of the subjects had anti-HB antibody concentrations ≥ 10 mIU/ml and 92.0% had anti-HB antibody concentrations ≥ 100 mIU/ml. An anamnestic response to the HBV vaccine challenge was observed in 95.7% of subjects.
- The HBV vaccine challenge dose was well tolerated. Grade 3 solicited symptoms were reported for only 1% of subjects. No SAEs were reported.

Response to the hepatitis B challenge dose (ATP immunogenicity cohort):

- Prior to administration of the HBV vaccine challenge dose, 86.0% of subjects had seroprotective levels of anti-HBs antibodies and 53.8% had anti-HBs antibody concentrations ≥ 100 mIU/ml.
- A strong response to the HBV challenge, with observation of a 83-fold increase in anti-HBs GMC, indicative of the presence of immune memory was observed. One month after the HBV vaccine challenge dose, 98.4% of the subjects had anti-HBs antibody concentrations ≥ 10 mIU/ml and 92.0% had anti-HBs antibody concentrations ≥ 100 mIU/ml.
- Overall, 95.7% of the subjects mounted an anamnestic response to the HBV vaccine challenge.

Synopsis table 2: Percentage of subjects with anti-HBs antibody concentrations of at least 10 mIU/ml, at least 100 mIU/ml and geometric mean concentrations (GMC) before and one month after the challenge dose (ATP cohort for immunogenicity).

				≥ 3.3 mIU/ml				≥ 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
All subjects		Pre	186	169	90.9	85.8	94.6	160	86.0	80.2	90.7	100	53.8	46.3	61.1	95.5	71.5	127.7
		Post	188	186	98.9	96.2	99.9	185	98.4	95.4	99.7	173	92.0	87.2	95.5	7904.3	5611.5	11133.9
Primary-086 (2,4,6 m)	Infanrix hexa alone	Pre	67	66	98.5	92.0	100	61	91.0	81.5	96.6	42	62.7	50.0	74.2	180.4	113.7	286.3
		Post	68	68	100	94.7	100	68	100	94.7	100	64	94.1	85.6	98.4	10125.2	5908.2	17351.9
Primary-078 (3,4,5m)	Infanrix hexa alone	Pre	51	46	90.2	78.6	96.7	45	88.2	76.1	95.6	30	58.8	44.2	72.4	109.8	63.8	189.0
		Post	52	51	98.1	89.7	100	50	96.2	86.8	99.5	49	94.2	84.1	98.8	11255.7	5778.6	21923.9
	Infanrix hexa + Prevnar	Pre	68	57	83.8	72.9	91.6	54	79.4	67.9	88.3	28	41.2	29.4	53.8	46.0	28.6	73.9
		Post	68	67	98.5	92.1	100	67	98.5	92.1	100	60	88.2	78.1	94.8	4709.0	2593.1	8551.5

Primary-086=Subjects who received their primary vaccination course in study 217744/086
Primary-078=Subjects who received their primary vaccination course in study 217744/078
Pre: Prior to the administration of challenge dose; Post: One month after the challenge dose
GMC = geometric mean antibody concentration, calculated for all subjects. Antibody concentrations below the cut-off of 3.3 mIU/ml were given an arbitrary value of one half the cut-off for the purpose of calculating the GMC.
N = number of subjects with available results; n (%) = number (percentage) of subjects with antibody concentrations above the specified cut-off; 95% CI; LL, UL = exact 95% confidence interval; lower and upper limits

DTPa-HBV-IPV-112

- **Primary objective:** To assess the anti-HBs antibody response to a challenge dose of HBV vaccine (*Engerix-B Kinder*) in subjects at 4-5 years of age, previously vaccinated with four doses of Infanrix hexa in the first two years of life.
- **Conclusions (Table 2 and 3):** Persisting seroprotective anti-HBs antibody concentrations were observed in 85.3% of 4 to 5-year-old children vaccinated in infancy with 4 doses of Infanrix hexa in routine clinical practice.
- A strong increase in anti-HBs GMC (103-fold) was observed in response to the HBV vaccine challenge.
- One month after administration of the HBV vaccine challenge, 98.6% of the subjects had anti-HBs antibody concentrations ≥ 10 mIU/ml and 95.8% had anti-HBs antibody concentrations ≥ 100 mIU/ml. An anamnestic response was observed in 96.8% of subjects.
- No SAE was reported during the study.

Response to the Hepatitis B challenge (ATP immunogenicity cohort):

One month after the HBV challenge dose:

- A strong response to the challenge dose was observed with a 103-fold increase in anti-HBs GMC, indicative of the presence of immune memory.
- Seroprotective concentrations of anti-HBs antibodies (anti-HBs antibody concentrations ≥ 10 mIU/ml) were seen in 98.6% of the subjects.
- More than 95% of the vaccinees had anti-HBs antibody concentrations ≥ 100 mIU/ml.
- Overall, 96.8% of the subjects mounted an anamnestic response to the HBV vaccine challenge.

Synopsis table 2: Percentage of subjects with anti-HBs antibody concentrations of at least 3.3 mIU/ml, at least 10 mIU/ml, at least 100 mIU/ml and GMC before and one month after the challenge dose (ATP cohort for immunogenicity).

		≥ 3.3 mIU/ml				≥10 mIU/ml				≥ 100 mIU/ml				GMC		
				95% CI				95% CI				95% CI			95% CI	
Timing	N	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	value	LL	UL
PRE	285	264	92.6	89.0	95.4	243	85.3	80.6	89.2	134	47.0	41.1	53.0	83.7	66.8	104.9
POST	286	284	99.3	97.5	99.9	282	98.6	96.5	99.6	274	95.8	92.8	97.8	8656.1	6560.7	11420.9

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 = Prior to the administration of challenge dose
POST = One month after the challenge dose

Synopsis table 3: Anamnestic response to the HBV challenge (ATP cohort for Immunogenicity)

		Anamnestic response			
				95% CI	
Pre-challenge status	N	n	%	LL	UL
S-	21	17	81.0	58.1	94.6
S+	264	259	98.1	95.6	99.4
Total	285	276	96.8	94.1	98.5

S- = seronegative subjects (antibody concentration < 3.3 mIU/ml for anti-HBs) prior to vaccination
S+ = seropositive subjects (antibody concentration ≥ 3.3 mIU/ml for anti-HBs) prior to vaccination
Total = subjects either seropositive or seronegative at pre-challenge
Response defined as:
For initially seronegative subjects, antibody concentration ≥ 10 mIU/ml at one month post challenge time point
For initially seropositive subjects: antibody concentration at one month post challenge time point ≥ 4 fold the pre-vaccination antibody concentration
N = number of subjects with both pre- and post-vaccination results available
n (%) = number (percentage) of responders
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit

4. Rapporteur's Overall Conclusion AND RECOMMENDATION

4.1. Overall conclusion

A total of 9 studies evaluating the commercial formulation of Infanrix Hexa are included in the current report. Of these, four studies evaluated safety and immunogenicity of the Infanrix Hexa vaccine in primary immunization studies (116, 106, 100 and 109) or booster vaccination studies (120 and 117). Study 120 and 117 are the booster studies of primary studies 116 and 109, respectively. Three studies, 110, 111 and 112, are antibody persistence studies. Reactogenicity and immunogenicity data of the primary and booster studies are not different from those reported in initial studies. Results of the antibody persistence studies show that persisting antibodies were present in 4 to 9 year old children vaccinated during infancy with 4 doses of Infanrix Hexa and these data are in line with what was reported in previous studies.

4.2. Recommendation

No further action required.