15 September 2016
EMA/719044/2016
Human Medicines Development and Evaluation

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/P46/120

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:

Stand-alone submission of the final study report for study 112921 (10PN-PD-DIT-050), in accordance with Article 46 of Regulation (EC) No 1901/2006. A short critical expert overview has been provided. The Company concluded that currently no changes to the Product Information of Infanrix hexa are needed.

Previous clinical trials have shown an increase in the incidence of fever (rectal temperature ≥38.0 C) in infants following the co-administration of pneumococcal conjugate vaccines with standard infant vaccines compared to infants that receive either the pneumococcal conjugate vaccine or standard infant vaccines separately. Another study showed that the use of paracetamol as prophylactic antipyretic treatment could prevent and reduce the incidence of febrile reactions, in intensity and/or duration, following pneumococcal conjugate vaccination, co-administered with standard infant vaccines.

However, lower immune responses to the 10Pn-PD-DiT vaccine (Synflorix) and to some of the co-administered antigens were observed in the group that received prophylactic paracetamol treatment to prevent febrile reactions. For all vaccine pneumococcal serotypes, lower antibody Geometric Mean Concentrations (GMCs) were observed one month post-primary and post-booster vaccination in the group receiving prophylactic paracetamol treatment compared to the non-antipyretic group. The same tendency was observed for antibodies against diphtheria, tetanus, pertactin (PRN) and polyribosylribitol phosphate (PRP) antigens after primary vaccination. After booster vaccination, this tendency was only observed for antibodies against tetanus. However, the seropositivity or seroprotection rates were not impacted and remained in line with previous experiences with Diphtheria-Tetanus-acellular Pertussis (DTPa)-based or pneumococcal vaccines with the exception of serotype 6B after primary vaccination [Prymula, 2009]. As a consequence, prophylactic administration of antipyretic drugs at the time of vaccination should not be routinely recommended since antibody responses to several vaccine antigens were reduced.

For Synflorix, section 4.4 of the SmPC and corresponding section of the PL were updated in order to reflect results from study 10PN-PD-DIT-050[1] which aimed to determine whether ibuprofen given prophylactically, significantly impacts the immune response in children receiving primary vaccination with Synflorix, co-administered with DTPa-combined vaccines, at 3, 4 and 5 months of age and a booster dose at 12-15 months of age. The impact of antipyretics on the incidence of febrile reactions and other safety and reactogenicity parameters was evaluated as well. In this study, there were no effects of prophylactic ibuprofen administration, either delayed or immediate, on the immune responses to Synflorix, or the routine childhood vaccines given concomitantly with Synflorix. The same conclusions can be drawn for both primary and booster vaccinations. In agreement with other studies, there was a reduction of immune responses when prophylactic paracetamol was administered either immediately, or delayed, both to Synflorix, and to some concomitant vaccine antigens of Infanrix hexa.

The primary safety outcome in this study was fever. There were no beneficial effects of immediate administration of ibuprofen compared to no ibuprofen in terms of fever reduction, and a trend towards fever reduction in delayed ibuprofen administration. There were no new safety signals, and the overall safety profile was in agreement with previous studies.

[1] Procedure No. EMEA/H/C/000973/II/0092. EMA/804788/2014. 23 December 2014.

1.1. Steps taken for the assessment

Submission date:	23/06/2016
Start of procedure:	18/07/2016
CHMP Rapporteur's preliminary assessment report circulated on:	08/09/2016
CHMP Rapporteur's updated assessment report circulated on:	09/09/2016
CHMP opinion:	15/09/2016

2. Assessment of the post-authorisation measure PAM 112921, 10PN-PD-DIT-050, EudraCT 2010-019761-28

Methods :

Primary Objectives :

- To show that GSK 10-valent pneumococcal conjugate vaccine administered as a three dose primary vaccination course with immediate OR delayed prophylactic ibuprofen treatment is non-inferior to 10-valent pneumococcal conjugate vaccine without prophylactic ibuprofen treatment in terms of percentage of subjects with pneumococcal antibody concentrations ≤ 0.2 µg/mL, despite a statistically significant decrease in ELISA Geometric Mean Concentration (GMC).

  Criteria for each pair-wise group comparison (IIBU versus NIBU; DIBU versus NIBU) at one month after primary immunization:

  - *Non-inferiority was demonstrated if the upper limit (UL) of the two-sided 98.25% confidence interval (98.25%CI) (adjusted one-sided alpha = 0.875%) of the difference between groups (NIBU minus IIBU or DIBU), in terms of percentage of subjects with pneumococcal antibody concentrations ≤ 0.2 µg/mL, was lower than 10% for at least seven out of the 10 pneumococcal serotypes*
  - *A statistically significant decrease in GMC was established if the UL of the two-sided 99.8% CI (adjusted one-sided alpha = 0.11364%) for the GMC ratios (IIBU or DIBU over NIBU) was below 1 for at least one of the 10 vaccine pneumococcal serotypes or for protein D.*

Secondary objectives :

- To determine the percentage reduction in febrile reactions (rectal temperature ≥38.0°C) when immediate or delayed prophylactic ibuprofen treatment is administered compared to no prophylactic ibuprofen treatment, after primary vaccination with GSK Biologicals' 10-valent pneumococcal conjugate vaccine co-administered with DTPa-combined vaccines.

  Criteria for detection of febrile reduction:

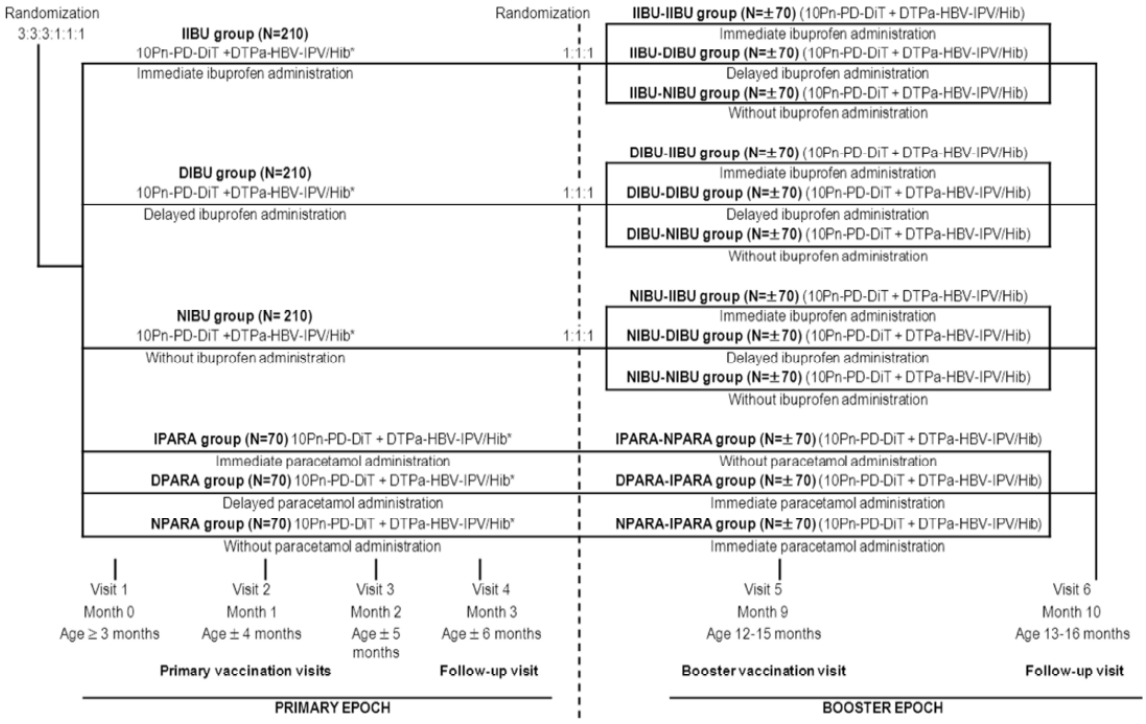
In order to control the type I error, the secondary objective was only assessable if the primary objective was met. A statistically significant reduction was demonstrated if the lower limit (LL) of the 97.5% CI around the difference (NIBU group minus IIBU group OR NIBU group minus DIBU group) in terms of percentage of subjects with fever ≥38°C (rectal temperature) within 4 days (Day 0-3) after at least one primary vaccine dose was higher than 0%.

- To assess the impact of immediate or delayed prophylactic paracetamol treatment on the immunogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine co-administered with DTPa-combined vaccines as a three-dose primary vaccination course.
- To assess the impact of immediate or delayed prophylactic paracetamol treatment on the incidence of febrile reactions (rectal temperature ≥38°C) after primary vaccination with GSK Biologicals' 10-valent pneumococcal conjugate vaccine co-administered with DTPa-combined vaccines.
- To assess the impact of immediate or delayed prophylactic ibuprofen treatment on the incidence of febrile reactions (rectal temperature ≥38°C) after booster vaccination with GSK Biologicals' 10- valent pneumococcal conjugate vaccine co-administered with DTPa-combined vaccine.
- To assess the impact of immediate prophylactic paracetamol treatment on the incidence of febrile reactions (rectal temperature ≥38°C) after booster vaccination with GSK Biologicals' 10-valent pneumococcal conjugate vaccine co-administered with DTPa-combined vaccine.
- To assess the impact of immediate or delayed prophylactic ibuprofen treatment on the safety and reactogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine and DTPa-combined vaccines, when administered as a three-dose primary vaccination course or as a booster dose.
- To assess the impact of immediate or delayed prophylactic paracetamol treatment on the safety and reactogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine and DTPacombined vaccines, when administered as a three-dose primary vaccination course.
- To assess the impact of immediate prophylactic paracetamol treatment on the safety and reactogenicity of a booster dose of GSK Biologicals' 10-valent pneumococcal conjugate vaccine and DTPa-combined vaccine.
- To assess, prior to booster vaccination, the impact of immediate or delayed prophylactic ibuprofen treatment on the persistence of antibodies induced by GSK Biologicals' 10-valent pneumococcal conjugate vaccine and DTPa-combined vaccines given as primary vaccination course.
- To assess, prior to booster vaccination, the impact of immediate or delayed prophylactic paracetamol treatment on the persistence of antibodies induced by GSK Biologicals' 10-valent pneumococcal conjugate vaccine and DTPa-combined vaccines given as primary vaccination course.
- To assess the impact of immediate or delayed prophylactic ibuprofen treatment on the immunogenicity of a booster dose of GSK Biologicals' 10-valent pneumococcal conjugate vaccine co-administered with DTPa-combined vaccine.

- To assess the impact of immediate prophylactic paracetamol treatment on the immunogenicity of a booster dose of GSK Biologicals' 10-valent pneumococcal conjugate vaccine co-administered with DTPa-combined vaccine.

Study design :

Phase IV, multicentre in Romania, open-label, randomized and controlled study.



* DTPa-IPV/Hib vaccine at 4 months of age (Visit 2)

Treatment allocation :

Internet-based randomization (SBIR) 3:3:3:1:1:1 into the different treatment groups (N = 210 for each of the three IBU groups or N = 70 for each of the three PARA groups) for primary vaccination. The three primary IBU groups were each randomized 1:1:1 into three subgroups (N = 70) at the time of booster vaccination. The three primary PARA groups (N = 70 each) were kept at the time of booster vaccination without sub-randomization but were assigned new antipyretic treatment.

Treatment:

The study groups were as follows:

Primary vaccination:

IBU groups:

- **IIBU** group (Immediate ibuprofen group): subjects receiving immediate ibuprofen administration after each primary vaccine dose (N = 210).
- **DIBU** group (Delayed ibuprofen group): subjects receiving delayed ibuprofen administration after each primary vaccine dose (N = 210).

- **NIBU** group (No ibuprofen group): subjects receiving no prophylactic ibuprofen administration after each primary vaccine dose (N = 210).

PARA groups:

- **IPARA** group (Immediate paracetamol group): subjects receiving immediate paracetamol administration after each primary vaccine dose (N = 70).
- **DPARA** group (Delayed paracetamol group): subjects receiving delayed paracetamol administration after each primary vaccine dose (N = 70).
- **NPARA** group (No paracetamol group): subjects receiving no prophylactic paracetamol administration after each primary vaccine dose (N = 70).

Booster vaccination:

IBU groups:

- **IIBU-IIBU** group: 1/3 of the subjects from the primary IIBU group receiving immediate ibuprofen administration after booster vaccination (N = 70).
- **IIBU-DIBU** group: 1/3 of the subjects from the primary IIBU group receiving delayed ibuprofen administration after booster vaccination (N = 70).
- **IIBU-NIBU** group: 1/3 of the subjects from the primary IIBU group receiving no prophylactic ibuprofen administration after booster vaccination (N = 70).
- **DIBU-IIBU** group: 1/3 of the subjects from the primary DIBU group receiving immediate ibuprofen administration after booster vaccination (N = 70).
- **DIBU-DIBU** group: 1/3 of the subjects from the primary DIBU group receiving delayed ibuprofen administration after booster vaccination (N = 70).
- **DIBU-NIBU** group: 1/3 of the subjects from the primary DIBU group receiving no prophylactic ibuprofen administration after booster vaccination (N = 70).
- **NIBU-IIBU** group: 1/3 of the subjects from the primary NIBU group receiving immediate ibuprofen administration after booster vaccination (N = 70).
- **NIBU-DIBU** group: 1/3 of the subjects from the primary NIBU group receiving delayed ibuprofen administration after booster vaccination (N = 70).
- **NIBU-NIBU** group: 1/3 of the subjects from the primary NIBU group receiving no prophylactic ibuprofen administration after booster vaccination (N = 70).

PARA groups:

- **IPARA-NPARA** group: subjects from the primary IPARA group receiving no paracetamol administration after booster vaccination (N = 70).
- **DPARA-IPARA** group: subjects from the primary DPARA group receiving immediate paracetamol administration after booster vaccination (N = 70).
- **NPARA-IPARA** group: subjects from the primary NPARA group receiving immediate paracetamol administration after booster vaccination (N = 70).

Treatment groups and vaccination schedule is shown in Table below. Of note, Infanrix hexa was given only at month 3 and 5 and at month 4, Infanrix-IPV/Hib, was given.

Primary vaccination at 3, 4, 5 months of age		Booster vaccination at 12-15 months of age	
IBU groups			
Group	Treatment	Group	Treatment
IIBU	10Pn-PD-DiT + DTPa-HBV-IPV/Hib* vaccine with immediate prophylactic ibuprofen administration after each vaccine dose: • Ibuprofen dose 1: administered at the time of vaccination • Ibuprofen dose 2 & 3: administered 6-8 hours after the previous dose	IIBU-IIBU	10Pn-PD-DiT + DTPa-HBV-IPV/Hib vaccine with immediate prophylactic ibuprofen administration after booster vaccination: • Ibuprofen dose 1: administered at the time of booster vaccination • Ibuprofen dose 2 & 3: administered 6-8 hours after the previous dose
		IIBU-DIBU	10Pn-PD-DiT + DTPa-HBV-IPV/Hib vaccine with delayed prophylactic ibuprofen administration after booster vaccination: • Ibuprofen dose 1: administered 4-6 hours after booster vaccination. • Ibuprofen dose 2 & 3: administered 6-8 hours after the previous dose
		IIBU-NIBU	10Pn-PD-DiT + DTPa-HBV-IPV/Hib vaccine with no prophylactic ibuprofen administration after booster vaccination
DIBU	10Pn-PD-DiT + DTPa-HBV-IPV/Hib* vaccine with delayed prophylactic ibuprofen administration after each vaccine dose: • Ibuprofen dose 1: administered 4-6 hours after vaccination. • Ibuprofen dose 2 & 3: administered 6-8 hours after the previous dose	DIBU-IIBU	10Pn-PD-DiT + DTPa-HBV-IPV/Hib vaccine with immediate prophylactic ibuprofen administration after booster vaccination: • Ibuprofen dose 1: administered at the time of booster vaccination • Ibuprofen dose 2 & 3: administered 6-8 hours after the previous dose
		DIBU-DIBU	10Pn-PD-DiT + DTPa-HBV-IPV/Hib vaccine with delayed prophylactic ibuprofen administration after booster vaccination: • Ibuprofen dose 1: administered 4-6 hours after booster vaccination. • Ibuprofen dose 2 & 3: administered 6-8 hours after the previous dose
		DIBU-NIBU	10Pn-PD-DiT + DTPa-HBV-IPV/Hib vaccine with no prophylactic ibuprofen administration after booster vaccination
NIBU	10Pn-PD-DiT + DTPa-HBV-IPV/Hib* vaccine with no prophylactic ibuprofen administration after each vaccine dose	NIBU-IIBU	10Pn-PD-DiT + DTPa-HBV-IPV/Hib vaccine with immediate prophylactic ibuprofen administration after booster vaccination: • Ibuprofen dose 1: administered at the time of booster vaccination • Ibuprofen dose 2 & 3: administered 6-8 hours after the previous dose
		NIBU-DIBU	10Pn-PD-DiT + DTPa-HBV-IPV/Hib vaccine with delayed prophylactic ibuprofen administration after booster vaccination: • Ibuprofen dose 1: administered 4-6 hours after booster vaccination. • Ibuprofen dose 2 & 3: administered 6-8 hours after the previous dose
		NIBU-NIBU	10Pn-PD-DiT + DTPa-HBV-IPV/Hib vaccine with no prophylactic ibuprofen administration after booster vaccination

PARA groups			
Group	Treatment	Group	Treatment

IPARA	10Pn-PD-DiT + DTPa-HBV-IPV/Hib* vaccine with immediate prophylactic paracetamol administration after each vaccine dose: • Paracetamol dose 1: administered at the time of vaccination • Paracetamol dose 2 & 3: administered 6-8 hours after the previous dose	**IPARA-NPARA**	10Pn-PD-DiT + DTPa-HBV-IPV/Hib vaccine with no prophylactic paracetamol administration after booster vaccination
DPARA	10Pn-PD-DiT + DTPa-HBV-IPV/Hib* vaccine with delayed prophylactic paracetamol administration after each vaccine dose: • Paracetamol dose 1: administered 4-6 hours after vaccination. • Paracetamol dose 2 & 3: administered 6-8 hours after the previous dose	**DPARA-IPARA**	10Pn-PD-DiT + DTPa-HBV-IPV/Hib vaccine with immediate prophylactic paracetamol administration after booster vaccination: • Paracetamol dose 1: administered at the time of booster vaccination • Paracetamol dose 2 & 3: administered 6-8 hours after the previous dose
NPARA	10Pn-PD-DiT + DTPa-HBV-IPV/Hib* vaccine with no prophylactic paracetamol administration after each vaccine dose	**NPARA-IPARA**	

* DTPa-IPV/Hib vaccine at 4 months of age (Visit 2)

Study population

Male or female infants between, and including, 12 and 16 weeks (84-118 days) of age at the time of the first vaccination, born after a gestation period of 36 to 42 weeks inclusive, free of obvious health problems as established by medical history and clinical examination before entering into the study and for whom the investigator believed that their parents/guardians could and would comply with the requirements of the protocol.

Primary Outcome / Efficacy Variable:

- Evaluation of immune responses to components of the investigational vaccine one month after primary immunization.
- Anti-pneumococcal antibody serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody concentrations ≥0.2 µg/mL.
- Concentrations of antibodies against the 10 vaccine pneumococcal serotypes.
- Concentrations of antibodies against protein D.

Secondary Outcome / Efficacy Variables:

Safety

- Occurrence of each solicited adverse event (AE) within 4 days (Days 0 to 3) after each primary vaccination dose and following booster vaccination.
    - Local (any, grade 3) AEs.
    - General (any, grade 3, related) AEs.
- Occurrence of unsolicited AEs within 31 days (Days 0 to 30) after each primary vaccination dose and following booster vaccination.
- Occurrence of serious adverse events (SAEs) during the entire study period.

Immunogenicity

- Evaluation of immune responses to components of the investigational vaccine for additional parameters, one month after primary immunization, prior to and one month after booster immunization:
    - Concentrations of antibodies against pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F.
    - Opsonophagocytic activity (OPA) against pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F*.
    - Concentrations of antibodies against protein D.
- Evaluation of immune responses to components of the co-administered DTPa-HBV-IPV/Hib and DTPa-IPV/Hib vaccines, one month after primary immunization, prior to and one month after booster immunization:
    - Antibody concentrations against diphtheria toxoid, tetanus toxoid, pertussis toxoid, filamentous haemagglutinin, pertactin, hepatitis B surface antigen*, polyribosylribitol phosphate.
    - Poliovirus types 1, 2 and 3 titres*.

**Note that the OPA, hepatitis B and polio results will be provided in an Annex Report.*

Statistical methods

Analysis of demographics

The analysis of demographics were performed separately for each epoch:

- Demographic characteristics (age in weeks at the time of each dose of primary vaccination and in months at the time of the booster dose, gender, weight, geographic ancestry) of each study cohort were tabulated.
- The mean age (plus range and standard deviation) of the enrolled subjects as a whole study population and per group was calculated.

Analysis of immunogenicity

The analysis of immunogenicity was performed separately for each epoch.

Within groups assessment

Where appropriate, for each group, at each timepoint that a blood sample result was available:

- Geometric Mean Concentrations/Titres (GMCs/GMTs) with 95% CIs were tabulated for each serotype/antigen.
- Seropositivity/seroprotection rates with exact 95% CIs were calculated for each appropriate serotype/antigen.
- Vaccine response rates one month post-dose III and one month post-booster dose with exact 95% CIs were calculated for each pertussis antigen.
- The distribution of antibody concentrations/titres for each appropriate serotype/antigen was displayed using tables and/or RCCs.

Between group assessment

Confirmatory inferential analysis

- Standardized asymptotic 98.25% CIs for the difference between groups (NIBU group minus IIBU group or NIBU group minus DIBU group), in terms of percentage of subjects with pneumococcal antibody concentrations ≥0.2 µg/mL one month post dose III, were computed using StatXact. The primary objective was demonstrated for one of the two pair-wise group comparisons if the UL of these two-sided 98.25% CIs was below 10% for seven out of the 10 vaccine pneumococcal serotypes.
- 99.8% CIs for the ELISA GMCs ratio (GMCs from the IIBU group over the GMCs from NIBU group OR GMCs from the DIBU group over the GMCs from NIBU group) one month post-dose III, was computed for each of the 10 conjugate vaccine pneumococcal serotypes and for protein D, using a one-sided ANOVA test on the logarithm10 transformation of the concentrations. A statistical significant difference in GMC was established if the UL of these two-sided 99.8% CIs was below 1 for at least one of the 10 vaccine pneumococcal serotypes or for protein D.

Analysis of safety

Analysis of safety relative to the primary epoch included analysis of safety data collected following administration of the three primary doses of study vaccine. Analysis of safety relative to the booster epoch included analysis of safety data collected following administration of the booster dose of study vaccine. At this second stage, in order to avoid missing SAEs that were reported, the SAE summary table included all events reported during the entire study period.

Within groups assessment

The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the 31-day (Day 0 - Day 30) postvaccination period was tabulated with exact 95% CI for each group, after each vaccine dose and overall primary doses. The percentage of doses followed by at least one local AE (solicited and unsolicited), by at least one general AE (solicited and unsolicited) and by any AE was tabulated for each group, over the full primary vaccination course, with exact 95% CI. The same calculations were performed for AEs rated as grade 3 and general AEs with causal relationship to vaccination.

The percentage of subjects reporting each individual solicited local and general AE during the 4-day (Day 0 - Day 3) post-vaccination period was tabulated for each group, after each vaccine dose and overall primary doses, with exact 95% CI. The percentage of doses followed by each individual solicited local and general AE was tabulated for each group, over the full primary vaccination course, with exact 95% CI. The same tabulation was performed for grade 3 solicited AEs and for solicited AEs with causal relationship to vaccination. For redness and swelling, grade 2 or 3 AEs were also tabulated. Occurrence of fever was reported per 0.5°C cumulative increments.

The proportion of subjects/doses with at least one report of unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA) and reported up to 30 days after primary or booster vaccination was tabulated with exact 95% CI for each group. The same tabulation was performed for grade 3 unsolicited AEs and for unsolicited AEs with a relationship to vaccination.

The proportion of AEs resulting in a medically attended visit was also tabulated.

The number and percentage of subjects who took concomitant antipyretic/medication at least once during the 4-day (Day 0 - Day 3) solicited follow-up period were tabulated for each group, after each vaccine dose and overall primary doses, with exact 95% CI. The number and percentage of doses for

which the subjects took concomitant antipyretic/medication at least once during the 4-day (Day 0 - Day 3) solicited follow-up period were tabulated for each group, over the full primary vaccination course, with exact 95% CI.

SAEs, large swelling reactions (after booster dose) and withdrawal(s) due to SAE(s) were described in detail.

Dosage of antipyretics taken and the summary of time interval between study vaccination and antipyretics were described in the groups receiving ibuprofen or paracetamol.

Between group assessment

Confirmatory inferential analysis:

Standardized asymptotic 97.5% CIs for the difference between groups (NIBU group minus IIBU group OR NIBU group minus DIBU group), in percentage of subjects reporting rectal temperature ≥38.0°C after at least one primary vaccination, were computed using StatXact.

The first secondary objective was demonstrated if the primary objective was reached and if the LL of the 97.5% CI around the difference NIBU group minus IIBU group OR if the LL of the 97.5% CI around the difference NIBU group minus DIBU group was higher than 0%.

Conduct of the study

During the course of the study, the following issues with regard to the conduct of the study were identified, either via site monitoring activities or were brought to GSK Biologicals' attention by other mechanisms. These issues were investigated and corrective/preventive actions where possible were taken as described below:

Following a letter notifying GSK about potential improper study conduct (), an assessment of this site was performed by the GSK's Global Quality Assurance group in March 2012. Following comparison of diaries from selected subjects, lack of confidence in the integrity of the data was noted. Additionally, there were concerns that the conduct of the informed consent process and documentation practices at the site did not meet the ICH-GCP requirements. Therefore GSK Biologicals decided to terminate all study-related activities at this site. Ethics Committee and Regulatory authorities were informed. All subjects a, who had not completed the study when site activities were put on hold, were withdrawn from the study and offered continuation of vaccination outside the study. All 35 subjects enrolled at this site were eliminated from the Total Vaccinated Cohort. Their blood samples were used to assess the immune response to allow individual counselling of the impacted study subjects. The SAEs reported for the subjects enrolled at this centre are presented separately.

Results :

This multi-centre study was conducted in 23 centers in Romania, however all 35 subjects from site were eliminated from the TVC (site closed after audit). Therefore the TVC included 812 subjects enrolled in 22 centers with a maximum of 210 subjects (25.9%) enrolled in a single study center. A summary of study continuation for subjection initially vaccinated in the primary epoch is presented in Table 21.

Table 21 Summary of study continuation for subjects initially vaccinated in the primary epoch (Primary epoch) (Total vaccinated cohort)

	IIBU N = 198		DIBU N = 198		NIBU N = 199		IPARA N = 71		DPARA N = 72		NPARA N = 74		Total N = 812	
Categories	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Permanent discontinuation during primary epoch	4	2.0	3	1.5	3	1.5	2	2.8	1	1.4	7	9.5	20	2.5
Not willing to participate in booster epoch	6	3.0	6	3.0	6	3.0	2	2.8	3	4.2	0	0.0	23	2.8
Consent withdrawal / not willing to participate, not due to a (S)AE	5	2.5	3	1.5	2	1.0	0	0.0	2	2.8	0	0.0	12	1.5
Lost to follow-up	0	0.0	2	1.0	1	0.5	1	1.4	1	1.4	0	0.0	5	0.6
Migrated / moved from the study area	1	0.5	1	0.5	3	1.5	1	1.4	0	0.0	0	0.0	6	0.7
Participating in booster epoch	188	94.9	189	95.5	190	95.5	67	94.4	68	94.4	67	90.5	769	94.7

Out of the 812 subjects vaccinated in the primary epoch, 792 completed the primary vaccination phase and 20 subjects were withdrawn. Among those, one subject was withdrawn due to an SAE assessed by the investigator as not related to vaccination.

Out of the 792 subjects who completed the primary vaccination phase, 768 were vaccinated during the booster epoch (note that with reference to Section 6.2.1, 769 subjects participated in the booster epoch but one subject did not receive the booster dose). Among those, 751 subjects completed the study and 17 did not complete the booster phase (one subject was withdrawn because of an SAE assessed by the investigator as not related to vaccination).

1. ***Immunogenicity results***

Non-inferiority of GSK Biologicals' 10-valent pneumococcal conjugate vaccine when administered as a three-dose primary vaccination course with immediate OR delayed prophylactic ibuprofen treatment in terms of percentage of subjects with pneumococcal antibody concentrations ≥0.2 µg/mL to 10-valent pneumococcal conjugate vaccine without prophylactic ibuprofen treatment for both pairwise group comparisons (IIBU versus NIBU; DIBU versus NIBU) was demonstrated since for nine out of 10 vaccine serotypes.

Assessor's comment:

Booster responses to the co-administered antigens follow the same pattern as the primary responses. As for the pneumococcal immune responses, no indication that ibuprofen diminishes the immune responses was seen. *The responses in the paracetamol receiving groups were slightly lower compared to the control group.* Overall, in this study, there were no effects of prophylactic ibuprofen administration, either delayed or immediate, in the immune responses to Synflorix, or the routine childhood vaccines given concomitantly with Synflorix. The same conclusions can be drawn for both primary and booster vaccinations. In agreement with other studies, there was a reduction of immune responses when prophylactic paracetamol was administered either immediately, or delayed, both to Synflorix, and to some concomitant vaccine antigens of Infanrix hexa.

2. ***Safety results***

- ***Between groups assessment***

The secondary confirmatory objective was to determine the percentage reduction in febrile reactions (rectal temperature ≥38.0°C) when immediate or delayed prophylactic ibuprofen treatment was administered compared to no prophylactic ibuprofen treatment, after primary vaccination with GSK Biologicals' 10-valent pneumococcal conjugate vaccine co-administered with DTPa-combined vaccines.

No statistically significant reduction in febrile reactions (rectal temperature ≥38.0°C) when immediate or delayed prophylactic ibuprofen treatment was administered compared to no prophylactic ibuprofen treatment after primary vaccination was demonstrated as the LL of the 97.5% CI around the

difference (NIBU group minus IIBU group and NIBU group minus DIBU group) in terms of percentage of subjects with fever ≥38°C within 4 days (Day 0-3) after at least one primary vaccine dose was not higher than 0% (-11.04% for the NIBU group minus IIBU group difference and -1.15% for the NIBU minus DIBU group difference).

Assessor's comment:

There was no difference in fever in the no ibuprofen and immediate ibuprofen, while there was a tendency towards lower fever incidence in the delayed ibuprofen group.

- ***Primary vaccination with 10Pn-PD-DiT vaccine and DTPa-(HBV)-IPV/Hib***

  - **Any symptom:** During the 31-day post-primary vaccination period, the overall/dose incidence of reported symptoms (solicited and/or unsolicited; local and/or general) ranged from 70.9% (DPARA group) to 85.2% (NPARA group).
  - **Solicited local symptoms:** During the 4-day post-primary vaccination period, redness was the most frequently reported solicited local symptom (overall/dose incidence ranged from 29.5% [DIBU group] to 41.7% [NPARA group]), whatever the injection site, except for the DPARA group where the most frequently reported solicited local symptom was pain (overall/dose incidence was 33.3%). The overall/dose incidence of reported solicited grade 3 local symptom was not higher than 4.2% [pain in the NPARA group], whatever the injection site.
  - **Solicited general symptoms:** During the 4-day post-primary vaccination period, irritability was the most frequently reported solicited general symptom (overall/dose incidence ranged from 35.6% [IPARA group] to 50.5% [NPARA group]), except for the IPARA group where the most frequently reported solicited general symptom was drowsiness (overall/dose incidence was 38.0%). The overall/dose incidence of grade 3 solicited general symptoms was not higher than 2.4% (irritability in the IPARA group). The incidence of solicited general symptoms with causal relationship to vaccination as assessed by the investigator ranged from 9.6% (loss of appetite in the IPARA group) to 33.4% (irritability in the NIBU group).
  - **Unsolicited symptoms:** During the 31-day post-primary vaccination period, at least one unsolicited symptom was reported after a maximum of 9.5% of doses (NPARA group). One grade 3 unsolicited symptom was reported after 0.2% of doses in the DIBU and NIBU groups and after 0.5% of doses in the IPARA group. At least one unsolicited symptom with causal relationship to vaccination was reported after 0.3% of doses in the IIBU group, after 0.5% of doses in the DIBU group and after 1.0% of doses in the IPARA group.

- ***Booster vaccination with 10Pn-PD-DiT vaccine and DTPa-HBV-IPV/Hib***

  - **Any symptom:** During the 31-day post-booster vaccination period, the incidence of reported symptom (solicited and/or unsolicited; local and/or general) ranged from 57.6% (IIBU-NIBU group) to 83.3% (NIBU-IIBU group).
  - **Solicited local symptoms:** During the 4-day post-booster vaccination period, pain and redness were the most frequently reported solicited local symptoms (incidence of pain ranged from 25.4% [IIBU-NIBU group] to 50.8% [NIBU-DIBU group] and incidence of redness ranged from 24.6% [DIBU-DIBU group] to 42.9% [IIBU-IIBU group]), whatever the injection site. Solicited grade 3 local symptom were reported for a maximum of 7.9% of subjects [redness in the NIBU-DIBU group], whatever the injection site. A large swelling reaction was reported

during the primary epoch for one subject from the NPARA-IPARA group one day after administration of the third dose of the 10Pn-PD-DiT vaccine.

- **Solicited general symptoms:** During the 4-day post-booster vaccination period, irritability was the most frequently reported solicited general symptom (incidence ranged from 32.8% [DPARAIPARA group] to 60.0% [NIBU-IIBU group]). Grade 3 solicited general symptoms were reported for a maximum of 5.1% of subjects (irritability in the IIBU-DIBU and DIBU-NIBU groups). The incidence of solicited general symptoms with causal relationship to vaccination as assessed by the investigator ranged from 6.8% (loss of appetite in the IIBU-NIBU group) to 45.0% (irritability in the NIBU-IIBU group).
- **Unsolicited symptoms:** During the 31-day post-booster vaccination period, at least one unsolicited symptom was reported for a maximum of 10.0% of subjects (IIBU-DIBU group). Two grade 3 unsolicited symptoms were reported: one for a subject (1.6%) in the IIBU-IIBU group and another for a subject (1.5%) in the IPARA-NPARA group. One unsolicited symptom with causal relationship to vaccination, which was of grade 3 intensity, was reported for a subject (1.6%) in the IIBU-IIBU group.
- **Serious adverse events: (Amended: 07 November 2014)**
    - One fatal SAE (craniocerebral injury) was reported for a subject from the Total enrolled cohort (DPARA group***;***) 132 days after the third dose and was considered by the investigator as not related to vaccination.
    - Among the subjects included in the TVC, at least one non-fatal SAE was reported for ***ten*** subjects during the primary epoch, for three subjects during the booster epoch and for ***two*** subjects during the period between both epochs. All SAEs recovered/resolved and were assessed by the investigator as not related to vaccination.
    - For subjects eliminated from the TVC), in addition to the fatal SAE, at least one non-fatal SAE was reported for three subjects during the period starting with the administration of study vaccine dose 1 up to the end of booster epoch. All SAEs recovered/resolved and were assessed by the investigator as not related to vaccination.
- **Withdrawals due to adverse events/serious adverse events:** Two subjects from the TVC were withdrawn due to an SAE during the study period. These events were considered as recovered/resolved and were assessed by the investigator as not related to vaccination.-

Assessor's comment:

The primary safety outcome in this study was fever. There were no beneficial effects of immediate administration of ibuprofen compared to no ibuprofen in terms of fever reduction neither in a trend towards fever reduction in delayed ibuprofen administration. There were no new safety signals, and the overall safety profile was in agreement with previous studies.

MAH Discussion

A. Study results of 10PN-PD-DIT-050

1. ***Ibuprofen effect on immune responses to 10Pn-PD-DiT and co-administered DTPacombined vaccines during primary and booster vaccination***

In summary, no clinically relevant impact of prophylactic administration of ibuprofen (immediate or delayed) at primary or booster vaccination on the immune response to pneumococcal, protein D and co-administered antigens (D, T, pertussis, Hib) was observed in this study.

2. ***Ibuprofen effect on reactogenicity following co-administration of 10Pn-PD-DiT and DTPa-combined vaccines***

No statistically significant reduction in febrile reactions (rectal temperature ≥38.0° C) during primary vaccination in subjects receiving immediate or delayed prophylactic ibuprofen administration compared to no prophylactic ibuprofen administration was demonstrated. The results indicate no impact of immediate prophylactic administration of ibuprofen on observed rate of post-primary vaccination fever.

No differences in reporting rates of fever following booster vaccination between prophylactic ibuprofen groups and no ibuprofen group were observed.

3. ***Paracetamol impact on immune responses to 10Pn-PD-DiT and co-administered DTPa-combined vaccines***

In the primary epoch, approximately 70 subjects were included in each of the PARA groups, while at the time of the booster epoch, approximately 50 subjects included in the PARA groups were assessed for immunogenicity.

Paracetamol used prophylactically during primary vaccination

Concerning co-administered vaccine antigens, for which the results were available (diphtheria, tetanus, pertussis [PT, FHA and PRN], Hepatitis B (HBV) and Hib PRP), immediate or delayed prophylactic administration of paracetamol during primary vaccination did not reveal major differences in seroprotection/seropositivity rates or antibody GMCs. The lowest GMC ratios were observed for anti-PRP (0.66) and anti-tetanus (0.78) in the group with immediate prophylactic paracetamol administration (IPARA versus NPARA) and for anti-tetanus (0.81) in the group with delayed prophylactic paracetamol administration (DPARA versus NPARA). While no antipyretics were given at booster dose, a trend for decreased post-booster antibody GMCs for majority of co-administered vaccine antigens was observed with no impact on seroprotection/seropositivity rates.

Paracetamol used prophylactically during booster vaccination

Concerning co-administered vaccine antigens, for which the results were available (diphtheria, tetanus, pertussis [PT, FHA and PRN], Hepatitis B (HBV) and Hib PRP), immediate prophylactic administration of paracetamol at booster seems to reduce antibody GMCs to some antigens (e.g. PT), however seroprotection rates and seropositivity rates remained high (⩾95.5%).

4. ***Paracetamol effect on reactogenicity following co-administration of 10Pn-PD-DiT and DTPa-combined vaccines***

With regard to fever, no major differences between paracetamol groups and control groups were observed during primary vaccination (overall/subject). However, a trend for decrease in rate of reported fever after at least one vaccine dose during primary vaccination was observed in the groups receiving immediate or delayed paracetamol administration (32.9% and 38.0% of subjects, respectively) versus control group (no paracetamol) (54.1% of subjects) (overall/subject).

Immediate prophylactic administration of paracetamol after the booster dose (only at booster dose or after delayed prophylactic administration of paracetamol during primary vaccination) tended to reduce fever (28.1% and 20.9% of subjects with fever in the NPARA-IPARA and DPARA-IPARA groups, respectively, versus 45.9% of subjects in the control NIBU-NIBU group.

5. Results limitations of the 10PN-PD-DIT-050 study

The group comparisons in exploratory analyses should be interpreted with caution considering that there was no adjustment for multiplicity of comparisons and that the clinical relevance of any differences remains unknown.

B. Study results in context of other publications

By the time of the MAH report finalisation, several publications presenting the results of the clinical trials assessing impact of antipyretics on immunogenicity and reactogenicity of various paediatric vaccines have become available. Short overview of the key findings from these studies is presented below. For further details refer to the publications.

1. ***GSK's studies 10PN-PD-DIT-010 and -014 assessing immediate prophylactic paracetamol treatment during primary and booster vaccination with 10Pn-PD-DiT and DTP-HBV-IPV/Hib vaccines [Prymula, 2009]:***
   - Lower immune responses to the 10Pn-PD-DiT vaccine and to some of the coadministered antigens were observed in the group that received prophylactic paracetamol treatment to prevent febrile reactions.
   - For all vaccine pneumococcal serotypes, lower antibody GMCs were observed one month post-primary and post-booster vaccinations in the group receiving prophylactic paracetamol treatment compared to the non-antipyretic group.
   - The same tendency was observed for antibodies against diphtheria, tetanus, pertactin (PRN) and polyribosylribitol phosphate (PRP) antigens after primary vaccination. After booster vaccination, this tendency was only observed for antibodies against tetanus.
   - However, the seropositivity or seroprotection rates were not impacted and remained in line with previous experiences with DTPa-based or pneumococcal vaccines with the exception of serotype 6B after primary vaccination.

2. ***Pfizer's study assessing paracetamol and ibuprofen impact (given in immediate and delayed manner each) during primary vaccination with PCV13 and DTP-HBVIPV/ Hib vaccines*** [Wysocki, International Symposium on Pneumococci and Pneumococcal Diseases 2014, abstract number: ISPPD-0238]. These are preliminary results:
   - Prophylactic paracetamol may interfere with infant series immune response to pneumococcal antigens.
   - Ibuprofen did not interfere with pneumococcal responses, but may reduce responses to pertussis FHA and tetanus antigens.
   - These effects are particularly apparent when antipyretic prophylaxis is administered at the time of vaccination.
   - These effects were not observed after a toddler dose.
   - The clinical significance of these findings is unclear but suggests that antipyretic prophylactic should be given careful consideration in the setting of infant vaccination.

3. ***Novartis' study assessing immediate paracetamol impact (given in immediate and delayed manner) during primary vaccination with multicomponent meningococcal serogroup B vaccine (4CMenB) co-administered with routine vaccinations (DTaPHBV-IPV/Hib and PCV7) [Prymula, 2014***].
   - The results from part of a phase 2, randomized, clinical trial show that prophylactic paracetamol in infants decreases fever and reactogenicity with no apparent clinically relevant impact on immune responses to the multicomponent meningococcal serogroup B vaccine (4CMenB), nor the concomitantly administered routine vaccinations (DTaP-HBV-IPV/Hib and PCV7).
   - The administration of oral paracetamol at the time of vaccination, with 2 subsequent doses at 4–6 h intervals, significantly reduced the incidence of febrile reactions ⩾ 38.5°C over 7 days post-vaccination, and fewer infants experienced solicited local reactions.
   - The proportion of infants experiencing any fever was lowered by 51–65% by paracetamol prophylaxis, and reports of rectal temperature >39.5 °C after any the 3-dose primary series were noticeably less common.

MAH Conclusions

Overall our study results showed no clinically relevant impact of prophylactic administration of ibuprofen (immediate or delayed) during primary or booster vaccination on the immune response to pneumococcal and to co-administered antigens (D, T, pertussis, HBV, Hib). This seems to be in agreement with preliminary findings of *Pfizer's* study. In addition, no significant decrease in febrile reactions or in reporting of safety/reactogenicity after prophylactic administration of ibuprofen was observed in our study.

Impact of prophylactic immediate or delayed administration of paracetamol on immune responses to PCV and DTP-combined vaccines antigens and on fever rates during priming seemed to be in line with the findings of the previous GSK's study and *Pfizer's* study, but detailed scope and magnitude of antipyretic impact varied. In the current study, trends of reduction on immune responses for delayed paracetamol administration were observed, but less pronounced than for immediate administration.

Compared to no prophylactic antipyretics administration during primary and booster vaccinations, immediate prophylactic administration of paracetamol only at booster did not reveal clinically relevant differences of immune response suggesting that paracetamol can be used for prophylaxis of febrile reactions/convulsions when a booster dose is given in the 2nd year of life.

Assessor's comment:

The Assessor agrees in general on the discussion and overall conclusions of the Applicant. Meanwhile the SmPC of Infanrix hexa should be consistent and in line with the one of Synflorix concerning section 4.4 , 4.5 which contain specific wordings on antipyretics and its impact as well as the recommendations formulated.

3. Rapporteur's overall conclusion

Overall, the results of study 10PN-PD-DIT-050 showed no clinically relevant impact of prophylactic **ibuprofen** during primary or booster vaccination on the immune response to the co-administered antigens included in Infanrix hexa except for polio (too low number of subjects with available results. Also, no ibuprofen effect on febrile reactions or in reporting of safety/reactogenicity. Impact of prophylactic immediate or delayed administration of **paracetamol** on immune responses to Infanrix

hexa combined antigens and on fever rates during primary immunization seemed in line with the findings of previous GSK studies 10PN-PD-DIT-010 and -014 assessing immediate prophylactic paracetamol treatment during primary and booster vaccination with 10Pn-PD-DiT and DTP-HBV-IPV/Hib vaccines [Prymula, 2009].

The procedure Infanrix hexa variation type II EMEA/H/C/000296/II/0177 amended the Product Information (PI) of Infanrix hexa to include information on co-administration with several paediatric vaccines. Meanwhile, the use of antipyrectics was not discussed at that time.

The Assessor considers the Applicant's discussion and conclusions as acceptable. The currently submitted study results do not change the B/R of Infanrix hexa. Nevertheless, in the interest of the patient and the HCP, the current SmPC and PIL should be UPDATED in line with the wordings provided in the SmPC of Synflorix concerning the antipyretics use, the impact on the immune response and the safety/reactogenicity as well as on the derived recommendations (please refer to Appendix 1 for overview of the current wordings of the SmPCs on those 2 items).

The Assessor requests a type II variation in which all data are reviewed and modifications to the SmPC are proposed, in line with Synflorix.

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

☒ PAM not fulfilled (not all commitments fulfilled) and further action required:

The Assessor requests a type II variation in which all data are reviewed (immunogenicity data of the Infanrix hexa antigens in primo/booster immunization when co-administered with Synflorix) and modifications to the SmPC are proposed, in line with the PI of Synflorix concerning the use of antipyretics and the eventual recommendations needed.

4. Appendix 1

In the current SmPC of Synflorix compared to Infanrix hexa (as of 6th Sept. 2016) :

Synflorix SmPC	***Infanrix hexa SmPC***
Section 4.4 Prophylactic administration of antipyretics before or immediately after vaccine administration can reduce the incidence and intensity of post-vaccination febrile reactions. Clinical data generated with paracetamol and ibuprofen suggest that the prophylactic use of paracetamol might reduce the fever rate, while prophylactic use of ibuprofen showed a limited effect in reducing fever rate. The clinical data suggest that paracetamol might reduce the immune response to Synflorix. However, the clinical relevance of this observation is not known. The use of prophylactic antipyretic medicinal products is recommended: - for all children receiving Synflorix simultaneously with vaccines containing whole cell pertussis because of higher rate of febrile reactions (see section 4.8). - for children with seizure disorders or with a prior history of febrile seizures. Antipyretic treatment should be initiated according to local treatment guidelines.	Section 4.4 The physician should be aware that the rate of febrile reactions is higher when Infanrix hexa is co-administered with a pneumococcal conjugate vaccine (PCV7, PCV10, PCV13), or with a measles-mumps-rubella-varicella (MMRV) vaccine, compared to that occurring following the administration of Infanrix hexa alone. These reactions were mostly moderate (less than or equal to 39°C) and transient (see sections 4.5 and 4.8). Increased reporting rates of convulsions (with or without fever) and hypotonic hyporesponsive episode (HHE) were observed with concomitant administration of Infanrix hexa and Prevenar 13 (see section 4.8). Antipyretic treatment should be initiated according to local treatment guidelines.
Section 4.5 Use with other vaccines Synflorix can be given concomitantly with any of the following monovalent or combination vaccines [including DTPa-HBV-IPV/Hib and DTPw-HBV/Hib]: diphtheria-tetanus-acellular pertussis vaccine (DTPa), hepatitis B vaccine (HBV), inactivated polio vaccine (IPV), Haemophilus influenzae type b vaccine (Hib), diphtheria-tetanus-whole cell pertussis vaccine (DTPw), measles-mumps-rubella vaccine (MMR), varicella vaccine (V), meningococcal serogroup C conjugate vaccine (CRM197 and TT conjugates), meningococcal serogroups A, C, W-135 and Y conjugate vaccine (TT conjugate), oral polio vaccine (OPV) and oral rotavirus vaccine. Different injectable vaccines should always be given at different injection sites. Clinical studies demonstrated that the immune responses and the safety profiles of the co-administered vaccines were unaffected, with the exception of the inactivated poliovirus type 2 response, for which inconsistent results were observed across studies (seroprotection ranging from 78% to 100%). In addition when the meningococcal serogroups A, C, W-135 and Y vaccine (TT conjugate) was co-administered with a booster dose of Synflorix during the second year of life in children primed with 3 doses of Synflorix, lower antibody geometric mean concentration (GMC) and opsonophagocytic assay geometric mean titre (OPA GMT) were observed for one pneumococcal serotype (18 C). There was no impact of co-administration on the other nine pneumococcal serotypes. Enhancement of antibody response to Hib-TT conjugate,	Section 4.5 Infanrix hexa can be given concomitantly with pneumococcal conjugate vaccine (PCV7, PCV10 and PCV13), meningococcal serogroup C conjugate vaccine (CRM197 and TT conjugates), meningococcal serogroups A, C, W-135 and Y conjugate vaccine (TT conjugate), oral rotavirus vaccine and measles-mumps-rubella-varicella (MMRV) vaccine. Data have shown no clinically relevant interference in the antibody response to each of the individual antigens, although inconsistent antibody response to poliovirus type 2 in co-administration with Synflorix was observed (seroprotection ranging from 78% to 100%) and the immune response rates to the PRP (Hib) antigen of Infanrix hexa after 2 doses given at 2 and 4 months of age were higher if co-administered with a tetanus toxoid conjugate pneumococcal or meningococcal vaccine (see section 5.1). The clinical relevance of these observations remains unknown.

diphtheria and tetanus antigens was observed. The clinical relevance of the above observations is unknown. Use with prophylactic administration of antipyretics See section 4.4.	Data from clinical studies indicate that, when Infanrix hexa is co-administered with pneumococcal conjugate vaccine, the rate of febrile reactions is higher compared to that occurring following the administration of Infanrix hexa alone.
Section 4.8	Section 4.8 Experience in co-administration: Analysis of postmarketing reporting rates suggests a potential increased risk of convulsions (with or without fever) and HHE when comparing groups which reported use of Infanrix hexa with Prevenar 13 to those which reported use of Infanrix hexa alone. In clinical studies in which some of the vaccinees received Infanrix hexa concomitantly with Prevenar (PCV7) as a booster (4th) dose of both vaccines, fever ≥ 38.0°C was reported in 43.4% of infants receiving Prevenar and Infanrix hexa at the same time as compared to 30.5% of infants receiving the hexavalent vaccine alone. Fever ≥39.5°C was observed in 2.6% and 1.5% of infants receiving Infanrix hexa with or without Prevenar, respectively (see sections 4.4 and 4.5). The incidence and severity of fever following co-administration of the two vaccines in the primary series was lower than that observed after the booster dose. According to different studies, immune response to the PRP antigen of Infanrix hexa after 2 doses given at 2 and 4 months of age will vary if co-administered with a tetanus toxoid conjugate vaccine. Infanrix hexa will confer an anti-PRP immune response (cut-off ⩾ 0.15 µ g/ml) in at least 84% of the infants. This rises to 88% in case of concomitant use of pneumococcal vaccine containing tetanus toxoid as carrier and to 98% when Infanrix hexa is co-administered with a TT conjugated meningococcal vaccine (see section 4.5).
Synflorix PIL	Infanrix hexa PIL
Your doctor may ask you to give your child a medicine that lowers fever (such as paracetamol) before or immediately after Synflorix is given. This can help to lower some of the side effects (febrile reactions) of Synflorix. However if your child has received paracetamol before or immediately after Synflorix is given, the obtained levels of antibodies may be slightly reduced. It is not known whether the reduction in antibody levels has an impact on the protection against pneumococcal disease.	