EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 May 2015
EMA/CHMP/329785/2015 - adopted
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Hexyon	diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) and haemophilus influenzae type b (hib) conjugate vaccine (adsorbed)
Hexacima	diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) and haemophilus influenzae type b (hib) conjugate vaccine (adsorbed)
Hexaxim	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/xxxx/WS/0702

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Procedure No. EMEA/H/C/WS0702

Medicinal products authorised through the centralised procedure

Invented name:	International non-proprietary name/Common name:	Product-specific application number
Hexacima	diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) and haemophilus influenzae type b (hib) conjugate vaccine (adsorbed)	EMEA/H/C/002702/WS0702/0018
Hexyon	diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) and haemophilus influenzae type b (hib) conjugate vaccine (adsorbed)	EMEA/H/C/002796/WS0702/0021

Medicinal Products authorised through Art.58 procedure

Invented name:	International non-proprietary name/Common name:	Product-specific application number
Hexaxim	diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) and haemophilus influenzae type b (hib) conjugate vaccine (adsorbed)	EMEA/H/W/002495/WS0702/0027

Worksharing applicant (WSA): Sanofi Pasteur MSD SNC

Rapporteur(s) and type of application	
CHMP Rapporteur:	Jan Mueller-Berghaus
Rapporteur for WS procedure:	n/a
This application is in the area of:	Clinical
eCTD sequences related to the procedure:	Hexacima - 34 , 41, 42, 46; Hexyon – 37, 45, 46, 50; Hexaxim – 58, 65, 66, 70

Assessment Timetable / Steps taken for the assessment

Timetable	Dates
Start of procedure:	28 December 2014
CHMP Rapporteur Assessment Report	30 January 2015
CHMP comments	16 February 2015
Rapporteur Revised Assessment Report	19 February 2015
Request for supplementary information	26 February 2015
Submission of MAH responses	4 March 2015
CHMP Rapporteur's assessment report:	9 March 2015
Comments on CHMP Rapporteur's assessment report:	16 March 2015
Rapporteur Revised Assessment Report	20 March 2015
2nd Request for supplementary information:	26 March 2015
Submission of MAH responses	15 April 2015
Rapporteur Revised Assessment Report	20 April 2015
Comments on CHMP Rapporteur's assessment report:	11 May 2015
Opinion	21 May 2015

Table of contents

1. Background information on the procedure

1.1. Requested type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Sanofi Pasteur MSD SNC submitted to the European Medicines Agency on 9 December 2014 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

Pursuant to section 10 of the CHMP "Guideline on procedural aspects regarding a CHMP scientific opinion in the context of cooperation with the World Health Organisation (WHO) for the evaluation of medicinal products intended exclusively for markets outside the community" (EMEA/CHMP/5579/04), Sanofi Pasteur MSD SNC submitted to the EMA on 9 December 2014 an application for a variation[1] to the CHMP Scientific Opinion.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.5 and 5.1 of the SmPC in order to add the information on co-administration of the hexavalent vaccine with meningococcal serogroup C vaccine. The Package Leaflet is updated accordingly. The MAH/SOH took also the opportunity to make minor editorial changes throughout the PI.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics and Package Leaflet.

1.2. Rationale for the proposed change

In this application the MAH/SOH updated the SmPCs of Hexacima, Hexyon and Hexaxim based on the results of the HXM01C study assessing the immunogenicity and safety of the concomitant administration of the hexavalent vaccine when given with meningococcal serogroup C (MenC) vaccine at 2, 3 and 4 months of age in healthy infants during primary series immunisation.

This application also fulfils the below described REC:

Description	**Due Date**
The applicant will conduct a clinical study to assess the concomitant use of Hexyon with a monovalent conjugated meningococcal vaccine. The results of this study are expected by Q1/2015.	Q1 2015

As per Article 46 of Regulation (EC) No 1901/2006 this application fulfils the MAH obligation to submit MAH-sponsored studies involving the use of an authorised medicinal product in the paediatric population.

[1] Which corresponds, by analogy, to a Type II variation pursuant to Commission Regulation (EC) 1234/2008

2. Overall conclusion and impact on the benefit/risk balance

The immunogenicity and safety findings of study HXM01C support the concomitant administration of Hexaxim, Hexacima, Hexyon with a meningococcal serogroup C conjugate vaccine.

The data presented with this worksharing procedure are sufficient to implement the changes to the SmPC as suggested by the MAH/SOH.

The benefit-risk balance of Hexaxim, Hexacima, Hexyon, remains positive.

Scientific Summary for the EPAR

In this variation the Product information has been updated with the information that co-administration of the hexavalent vaccine with meningococcal serogroup C vaccine does not lead to any clinically relevant interference in the antibody response to each of the antigens.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.5 and 5.1 of the SmPC in order to add the information on co-administration of the hexavalent vaccine with meningococcal serogroup C vaccine. The Package Leaflet is updated accordingly. The MAH/SOH took also the opportunity to make minor editorial changes throughout the PI.

☒ is recommended for approval.

The requested worksharing procedure leads to amendments to the Summary of Product Characteristics and Package Leaflet.

4. Scientific discussion

4.1. Introduction

With this application the MAH/SOH intends to update the SmPCs of Hexacima, Hexyon and Hexaxim based on the results of the HXM01C study assessing the immunogenicity and safety of the concomitant administration of Hexyon given at 2, 3 and 4 months of age (MoA) with a meningococcal serogroup C conjugate (MenC) vaccine given at 2 and 4 MoA in healthy infants during primary series immunization.

This application fulfils the post-authorization measure REC of conduction of a clinical study to assess the concomitant use of Hexyon with a monovalent conjugated meningococcal vaccine by Q1/2015.

Remark:

Data comprise serology results from primary series vaccination only. Results from the booster part will be analysed in an extension to study HXM01C and described in a separate clinical study report.

4.2. Clinical Efficacy aspects

4.2.1. Methods – analysis of data submitted

Design: open-label, randomised, multi-centre study conducted in Finland between 29 April 2013 (FVFS) and 26 November 2013 (LVLS). During the study, 350 subjects, 46 to 74 days of age, born at full term of pregnancy (≥37 weeks) and/or with a birth weight ≥2.5 kg were randomised in a ratio 1:1 to receive Hexyon co-administered with MenC vaccine (Group 1) or Hexyon without MenC vaccine (Group 2). Both groups received routine vaccination with RotaTeq and Prevenar 13 (see **Table 1**).

Inclusion and exclusion criteria were state-of-the-art (for details, refer to HXM01C clinical study report).

Test vaccines:

- Hexyon: Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed), suspension for injection in a pre-filled syringe, 1 dose (0.5mL), intramuscular route
- MenC vaccine: Meningococcal Group C polysaccharide conjugate vaccine to tetanus toxoid (NeisVac-C; Baxter), suspension for injection, 1 dose (0.5mL), intramuscular route

Routine vaccines:

- Prevenar 13 (Pfizer): Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed), suspension for injection, 1 dose (0.5mL), intramuscular route
- RotaTeq (Sanofi Pasteur MSD): human-bovine rotavirus reassortants (live) vaccine, 1 dose (2mL) oral route

Table 1. Study design and vaccination group assignments

Visit	V1	V2	V3	V4
Age in months	**~ 2 months 46 to 74 days of age**	**~ 3 months**	**~ 4 months**	**~ 5 months**
Vaccination Group 1	Hexyon MenC vaccine	Hexyon	Hexyon MenC vaccine	
Vaccination Group 2	Hexyon	Hexyon	Hexyon	
Routine vaccinations for all subjects	RotaTeq® Prevenar 13®	RotaTeq®	RotaTeq® Prevenar 13®	
Blood sample (BS)	BS1	BS2 (only for Group 1)		BS3

Source: Clinical Study Report (CSR) of Study HXM01C, Table 9.1

RotaTeq was administered orally, the other vaccines were administered intramuscularly in the left (Hexyon) and right thigh (NeisVac-C and Prevenar 13). The two injections sites at the right thigh had to be separated by at least 5 cm.

Depending on study group, two to three blood samples (BS) of approximately 3 to 5 mL were collected from the subjects. Blood sampling was always performed before vaccination. The use of anaesthetic products was allowed for blood sampling (i.e. as prophylaxis against pain) if not contraindicated for the subject.

Serology tests for Hexyon antigens were performed by laboratory staff that was blinded for the group allocation.

Subjects were kept under observation at the investigators' sites for 30 minutes after each vaccination and any immediate adverse event had to be recorded.

For safety follow-up, the subjects' parents or legal representatives received a Diary Card (DC) at visit 1 to visit 3 and were informed on how to complete it. On the DC, the subjects' body temperature, the injection site and systemic reactions and unsolicited adverse events were to be recorded.

All serious adverse events and non-serious adverse events assessed as related to the study vaccine were to be followed up by the investigators until their complete resolution or stabilization.

Each subject was followed up for a period of about 3 to 4 months.

(Co-)Primary objectives:

- To demonstrate that the concomitant administration of Hexyon given at 2, 3 and 4 MoA with a MenC vaccine given at 2 and 4 MoA is non-inferior to the administration of Hexyon without a MenC vaccine concomitantly in terms of seroprotection rate for hepatitis B (HepB) 1 month after the third Hexyon dose.
- To demonstrate that the concomitant administration of a MenC vaccine given at 2 and 4 MoA with Hexyon given at 2, 3 and 4 MoA induces an acceptable response for MenC in terms of seroprotection rate 1 month after the second dose of MenC vaccine.

Secondary objectives:

- To describe the antibody response to all Hexyon antigens 1 month after the third dose when given concomitantly or not to MenC vaccine.
- To describe the antibody response to MenC vaccine when given concomitantly with Hexyon, 1 month after the first and the second dose of MenC vaccine.

Primary immunogenicity endpoints:

- Proportion of subjects with an anti-HepB concentration ≥10 mIU/mL (i.e. anti-HepB SPR);
- Proportion of subjects with an anti-MenC titer ≥8 (1/dil) (i.e. anti-MenC SPR).

Secondary immunogenicity endpoints:

(a) Hexyon (post-dose 3)

- Anti-HepB geometric mean titer (GMT)
- Anti-PRP geometric mean concentration (GMC) and proportion of subjects with an anti-PRP concentration ≥0.15 µg/mL
- Anti-D GMC and proportion of subjects with an anti-D concentration ≥0.01 IU/mL and ≥0.1 IU/mL
- Anti-T GMC and proportion of subjects with an anti-T concentration ≥0.01 IU/mL and ≥0.1 IU/mL
- Anti-IPV1, anti-IPV2 and anti-IPV3 GMTs and proportion of subjects with an anti-IPV1, anti-IPV2, and anti-IPV3 titer, respectively, ≥8 (1/dil)
- Anti-PT and anti-FHA GMC and proportion of subjects with an anti-PT and anti-FHA vaccine response

  with vaccine response defined as:

  - If pre-vaccination antibody concentration was <4xLLOQ, then the post-vaccination antibody concentration was to be ≥4xLLOQ,
  - If pre-vaccination antibody concentration was ≥4xLLOQ, then the post-vaccination antibody concentration was to be ≥pre-immunisation levels (=baseline).

(b) MenC

- Proportion of subjects with an anti-MenC titer ≥8 (1/dil) at post-dose 1
- Anti-MenC GMT and proportion of subjects with an anti-MenC titer ≥128 (1/dil) at post-dose 2

Table 2. Schedule of Immunogenicity Measurements

Vaccine component	Blood Sample 1 (Visit 1)	Blood Sample 2 (Visit 2) Group 1 only	Blood Sample 3 (Visit 4)
Meningococcal Serogroup C		**yes**	**yes**
HepB Antigen			**yes**
Hib (PRP)			**yes**
Pertussis (PT, FHA)	**yes**		**yes**
Diphtheria			**yes**
Tetanus			**yes**
Poliovirus types 1, 2 & 3			**yes**

Source: CSR of study HXM01C, Table 9.4 (adapted)

Table 3. Summary of Methods for Immunogenicity Measurement

Component	Assay	Abbreviation	LLOQ	Lab	Priority
Meningococcal serogroup C	Serum bactericidal assay using rabbit complement	rSBA	4 (1/dil.)	VEU	1
HepB antigen	Hep B enhanced chemiluminescence assay	HepB ECi	5 mIU/mL	GCI	1
Hib (PRP)	Radioimmunoassay	RIA	0.06 µg/ mL		2
Pertussis (PT, FHA)	Enzyme-linked immunosorbent assay	ELISA	2 EU/mL		3
Diphtheria	Micrometabolic inhibition test	MIT	0.005 IU/ mL		4
Tetanus	Enzyme-linked immunosorbent assay	ELISA	0.01 IU/ mL		5
Poliovirus types 1, 2 & 3	Micrometabolic inhibition test	MIT	4 (1/dil.)		6

VEU: Vaccine Evaluation Unit, Manchester, UK; GCI: Global Clinical Immunology, Swiftwater, PA, USA

Source: CSR of study HXM01C, Table 9.5

Statistical analysis:

The hypothesis for the first primary objective was that Hexyon administered concomitantly with the MenC vaccine (group 1) is non-inferior to Hexyon administered without MenC (group 2) in terms of HepB seroprotection rate (SPR; proportion of subjects with an anti-HepB concentration ≥10 mIU/mL) at 1 month post-dose 3.

- Non-inferiority was demonstrated if the two-sided 95% CI around the difference in SPR (group 1 – group 2) excluded a decrease of 10% or more (i.e. if the lower bound of the CI was greater than -10%).

The hypothesis for the second primary objective was that the SPR to MenC vaccine (proportion of subjects with an anti-MenC titer ≥8 [1/dil]) when administered concomitantly with Hexyon (group 1) was acceptable at 1 month post-dose 2.

- The seroprotection rate to MenC was considered acceptable if the lower bound of its two-sided 95% confidence interval (CI) was >90%.

Success for the study required that both primary objectives were achieved.

The choice of the acceptability margin and the non-inferiority margin was driven by the clinical relevance, the expected seroprotection rates/vaccine response rate, and the desired accuracy of the conclusions of the study. With 140 evaluable subjects in both groups (as per sample size assumptions) and assuming an anti-HepB SPR of 95% in the Hexyon group (as achieved in study A3L10 performed in Turkey), the largest observable difference in SPR which would lead to rejecting the null hypothesis of non-inferiority was 3.6% corresponding to an SPR of 91.4% in group 1 (Hexyon plus MenC).

With 140 evaluable subjects in each group for the primary analysis, assuming no difference between groups for the anti-HBs seroprotection rate and using a one-sided 2.5% type one error rate, the power of the study according to the expected response rates and the non-inferiority margin or acceptability thresholds were calculated as follows:

Table 4. Overall power calculation

Valence	Hypothesis	No. of evaluable subjects / group	Expected response rate	□	Margin or threshold	Power
Hep. B	non-inferiority	140	95%	2.5%	10%	92.6%
MenC	acceptability	140	98%	2.5%	90%	97.7%
Overall Power						~90.4%

Source: Table 9.9, HXM01C CSR

Assuming independence of the primary hypotheses, the overall power of the study was around 90% for the success of the primary objectives with 350 randomised subjects.

The immunogenicity analyses (primary and secondary objectives) were performed on the Per Protocol Set (PPS), defined as all randomized subjects excluding those with protocol violations (= main analysis). The analyses were repeated on the Full Analysis Set (FAS), defined as all randomized subjects who received at least one dose of the study vaccine(s) and with any post-vaccination immunogenicity evaluation (= supportive analysis).

With regards to the assays used for immunogenicity assessment, the endpoints analysed, and the timing of the serology assessment (i.e. 1 month [28 to 42 days] post-dose 3), the parameter were consistent with those used during the clinical development of Hexyon. Well-established seroprotection levels for diphtheria, tetanus, poliovirus, HepB and Hib were used to assess the immune responses to Hexyon (**Table 5**).

For pertussis antigens, for which no established correlates of protection are available, accepted surrogates of protection were applied (i.e., vaccine response rates).

The functional assay used for the MenC immunogenicity (rSBA) represents the one generally used for this type of vaccine.

Assessor's comment:

The assays used for immunogenicity analysis were consistent to those used in former clinical studies with Hexyon or MenC conjugate vaccines. Protection levels applied were established correlates (D, T, IPV, PRP, HepB, and MenC) or accepted surrogates of protection (PT, FHA).

Table 5. Correlates of protection and surrogates for protection applied in study HXM01C

Antigen	Antibody (Ab) Titer as Level of Protection	Assessment
Diphtheria	≥ 0.01 IU/mL (short-term) ≥ 0.1 IU/mL (long-term)	Established correlate
Tetanus	≥ 0.01 IU/mL (short-term) ≥ 0.1 IU/mL (long-term)	Established correlate
Polio 1, 2, 3	≥ 8 (1/dil)	Established correlate
PRP-T	≥ 0.15 µg/mL (short-term)	Established correlate
Hepatitis B	≥ 10 IU/mL	Established correlate
PT, FHA (pertussis)	**Vaccine Response:** - If pre-vaccination antibody concentration was <4x LLOQ, then the post-vaccination antibody concentration was to be ≥4xLLOQ; - If pre-vaccination antibody concentration was ≥4xLLOQ, then the post-vaccination antibody concentration was to be ≥pre-immunisation levels.	Accepted surrogate
MenC	≥ 8 (1/dil)	Established correlate

4.2.2. Results

Demography:

The two groups of subjects were comparable in terms of age, gender, ethnic origin, height, body weight and body temperature. Overall, the mean (SD) age of randomized infants at first vaccination was 63.0 days [range: 47-75 days], 52.9% were male and 92.6% were Caucasian. Mean weight was 5.5 kg (SD: 0.7 kg). The mean ages at each vaccination visit were comparable between the two groups. Overall, the mean age at vaccination visits 1, 2 and 3 was 63.0 days, 95.8 days and 128.9 days, respectively, and confirmed a 2, 3 and 4 month vaccination schedule.

Extent of exposure:

All 350 subjects randomized received the first dose of Hexyon, 347 subjects (99.1%) received the second dose and 346 subjects (98.9%) received the third dose.

Among the 175 subjects randomized to group 1 (Hexyon + MenC), 174 subjects (99.4%) received the first dose of MenC vaccine and 173 subjects (98.9%) received the second dose. One subject randomized to this group did not receive the MenC vaccine (both doses). One additional subject did not receive the second dose of MenC vaccine.

Among the 350 randomised subjects, 345 subjects (98.6%) completed the study. Five subjects (1.4%) were withdrawn from the study: 1 subject (0.6%) in the Hexyon + MenC group and 4 subjects (2.3%) in the Hexyon group. Reasons leading to withdrawals were adverse events (3 subjects, see under safety, section 4.3.2.) or lost to follow-up (2 subjects).

RotaTeq 1st dose was administered orally to all subjects, the 2nd dose to 347 subjects (99.1%) and the 3rd dose to 346 subjects (98.9%). All subjects received the 1st dose of Prevenar 13 and 347 subjects (99.1%) received the 2nd dose.

Table 6. Description of Immunogenicity Analysis Sets

	Hexyon + MenC (N=175) n (%)	Hexyon (N=175) n (%)	Total (N=350) n (%)
Randomized Set	175 (100%)	175 (100%)	350 (100%)
Full Analysis Set	174 (99.4%)	166 (94.9%)	340 (97.1%)
Per Protocol Set	162 (92.6%)	160 (91.4%)	322 (92.0%)

Source: Table 11.1, HXM01C CSR

Protocol deviations:

Overall, 28 subjects (8.0%) were excluded from the PPS due to protocol deviations: 13 subjects (7.4%) in the Hexyon + MenC group and 15 subjects (8.6%) in the Hexyon group (**Table 6.**). The most frequent deviations were non-compliance with the vaccination schedule (7 subjects in each group) and non-compliance with blood sampling schedule (6 and 8 subjects in the Hexyon + MenC and Hexyon group, respectively). One subject randomised to the Hexyon + MenC group was not vaccinated as per randomisation and did not receive the MenC vaccine.

RESULTS

Primary Immunogenicity Endpoints (PPS)

The HepB SPR (proportion of subjects with antibody concentrations ≥10 mIU/mL) observed one month after the 3rd dose was very similar in both groups, i.e., 97.5% in the Hexyon + MenC group and 96.1% in the Hexyon group (**Table 7**). The difference in SPR between the two groups was 1.4 %, the lower bound of the 95%CI of the difference was -2.92%, i.e. greater than the pre-specified non-inferiority margin of -10% (Table 7.). The analysis showed that the concomitant administration of Hexyon with MenC vaccine is non-inferior to the administration of Hexyon without MenC in terms of HepB SPR at 1 month post-dose 3.

Table 7. Non-inferiority analysis of post-dose 3 HepB SPR– PPS

Parameter	Group 1 Hexyon + MenC (N=162)	Group 2 Hexyon (N=160)	Difference Group 1 – Group 2	Non-inferiority (1)
Seroprotection rate				
n	160	155		
≥ 10 mIU/mL	156 (97.5%)	149 (96.1%)	1.37 %	
[95% CI]	[93.7;99.3]	[91.8;98.6]	[-2.92 ; 5.95]	Met

(1) Group 1 seroprotection rate was considered as non-inferior to group 2 SPR if the lower bound of the 95% CI of the difference was greater than -10%.

Source: Table11.7, HXM01C CSR

The percentage of subjects with MenC rSBA titers ≥8 (1/dil) at 1 month post-dose 2 was 100%. The lower bound of the 95%CI was 97.7% which is greater than the pre-specified acceptability threshold of 90% (**Table 8.**). Therefore, the concomitant administration of a MenC vaccine given at 2 and 4 MoA with Hexyon given at 2, 3 and 4 MoA induces a sufficient MenC response at 1 month after the 2nd MenC dose. The response is comparable to those achieved with MenC vaccine alone (see SmPC, NeisVac-C).

Table 8. Acceptability analysis of post-dose 2 MenC SPR– PPS

Parameter	Hexyon + MenC (N=162)	Acceptability (1)
Seroprotection rate		
n	162	
≥ 8 (1/dil)	162 (100.0%)	
[95% CI]	[97.7;100.0]	Met

(1) Seroprotection rate was considered as acceptable if the lower bound of the 95% CI was greater than the pre-specified acceptability threshold: 90%.

Source: Table11.8, HXM01C CSR

For both end points, comparable results were observed in the Full Analysis Set.

Assessor's comment:

Co-administration of Hexyon with MenC vaccine does not impact the infants' primary immune response to Hepatitis B with regard to HepB SPR (≥ 10 mIU/mL) at 1 month post-Hexyon dose 3.

Likewise, the MenC SPR (rSBA titers ≥8 [1/dil.]) at 1 month post-2nd dose was unaffected by co-administration of Hexyon (for comparison, see also SmPC of NeisVac-C).

Both co-primary objectives of study HXM01C were met.

It should be noted that in study HXM01C, immune responses to the routine vaccines (Rotateq, Prevenar 13) administered concomitantly to Hexyon and MenC had not been analysed. Concomitant use of these vaccines with Hexyon has, however, been proven in previous studies.

Secondary Immunogenicity Endpoints (PPS)

Post-Dose 1 and Post-Dose 2 Antibody Response to MenC vaccine

The MenC SPR was 99% after the 1st MenC dose and 100% after the 2nd dose at the pre-defined correlate of protection (≥ 8 [1/dil.]). 98 and 96% of subjects, respectively, achieved the higher (long-term) seroprotection level of 128 (1/dil.) at 1 month post-dose 1 and post-dose 2 (**Table 9.**). Geometric mean titers (GMT) lay at 885 after the 1st MenC dose and decreased to 580 after the second dose with non-overlapping CI. However, the 2nd MenC dose allowed for an SPR ≥ 8 [1/dil.] to be detected in every subject; the minmum GMT increased from 2 at post-dose 1 to 32 at post-dose 2.

Table 9. Post-dose 1 and post-dose 2 MenC response rate and GMT – PPS

Parameter	Hexyon + MenC (N=162)	
	Dose 1	**Dose 2**
MenC antibody response		
n	157	162
≥8 (1/dil)	156 (99.4%)	162 (100.0%)
[95% CI]	[96.5;100.0]	[97.7;100.0]
n	157	162
≥128 (1/dil)	154 (98.1%)	156 (96.3%)
[95% CI]	[94.5;99.6]	[92.1;98.6]
MenC antibody titer (1/dil)		
n	157	162
GMT	885.17	579.64
95% CI	[737.06;1063.04]	[505.36;664.84]
Min. ; Max.	2.00 ; 16384.00	32.00 ; 8192.00

Source: Table11.11, HXM01C CSR

Post-dose 3 immune response to Hexyon antigens

One month after the 3rd Hexyon dose, no notable differences were observed between both groups in terms of seroprotection rates/vaccine response rates for any Hexyon antigen (**Table 10.**).

Proportions of subjects showing antibody responses above the minimum or short-term level of protection (HepB ≥10 mIU/L, PRP ≥0.15 mg/mL, D and T ≥0.01 IU/mL) were high and comparable for both groups ranging from 96 to 100%.

Proportions of subjects with anti-D and anti-T ≥0.1 IU/mL (i.e., long-term protection levels) were also comparable for both groups. For diphtheria, the SPR rates at ≥0.1 IU/mL were low, i.e, 35% in the Hexyon + MenC group and 41% in the Hexyon group ; corresponding anti-D GMC lay at 0.08 and 0.09 IU/mL, respectively. Anti-D SPR and GMC were in the same range as those observed following primary vaccination with Hexyon in previous clinical studies, but should nevertheless be followed-up after booster vaccination to check for long-term protection of the subjects.

The GMCs observed for PRP and tetanus were higher in the Hexyon + MenC group compared to the Hexyon group (with non-overlapping CI; **Table 11.**). There is some trend for decreased GMC/GMT in the Hexyon + MenC group compared to Hexyon group for pertussis and IPV antigens and HepB, however with overlapping CI. For HepB, GMC at post-primary vaccination lay at 243 mIU/mL for Hexyon + MenC and at 268 mIU/mL for Hexyon, i.e. in the range of those found in previous primary vaccination studies using Hexyon. Levels are sufficient for the time interval until booster vaccination but insufficient with regard to

long-term protection. Booster response should thus be followed-up after booster vaccination of the subjects with Hexyon.

Comparable results were observed in the Full Analysis Set.

Assessor's comment:

Seroprotection rates / vaccine response rates as well as GMC/GMT after 3 doses of Hexyon co-administered with 2 doses of MenC (plus routine vaccines) were in the same range as those following Hexyon alone (plus routine vaccines). Following co-administration of MenC vaccine, increased GMC were found for PRP and tetanus, whereas GMC/GMT for most of the other Hexyon components were somewhat lower compared to Hexyon administered without MenC. However, both groups showed very similar SPR using established or surrogate levels of protection which supports the co-administration of Hexyon and MenC conjugate vaccine.

Although satisfying SPR were obtained, for diphtheria and HepB, GMC levels were low at 1 month-post primary dose 3. Levels are, however, in the range of those found in previous studies with Hexyon. Achievement of long-term protection levels should be followed up after booster vaccination.

Overall, data did not indicate any relevant interference between immune responses to Hexyon and MenC vaccine antigens following concomitant administration.

Table 10. Summary of post-dose 3 seroresponse rates for Hexyon antigens – PPS

		Hexyon + MenC (N=162)			Hexyon (N=160)		
Component	**Criteria**	**M**	**n (%)**	**95% CI**	**M**	**n(%)**	**95% CI**
Anti-HBs	≥10 mIU/mL	160	156 (97.5%)	[93.7;99.3]	155	149 (96.1%)	[91.8;98.6]
Anti-PRP	≥0.15 µg/mL	160	157 (98.1%)	[94.6;99.6]	158	149 (94.3%)	[89.5;97.4]
Anti-D	≥0.01 IU/mL	160	160 (100.0%)	[97.7;100.0]	158	157 (99.4%)	[96.5;100.0]
	≥0.10 IU/mL	160	56 (35.0%)	[27.6;42.9]	158	65 (41.1%)	[33.4;49.2]
Anti-T	≥0.01 IU/mL	159	159 (100.0%)	[97.7;100.0]	156	156 (100.0%)	[97.7;100.0]
	≥0.10 IU/mL	159	159 (100.0%)	[97.7;100.0]	156	155 (99.4%)	[96.5;100.0]
Anti-PT	Vaccine response*	154	152 (98.7%)	[95.4;99.8]	154	154 (100.0%)	[97.6;100.0]
	4-fold increase	154	136 (88.3%)	[82.2;92.9]	154	136 (88.3%)	[82.2;92.9]
Anti-FHA	Vaccine response*	154	153 (99.4%)	[96.4;100.0]	153	153 (100.0%)	[97.6;100.0]
	4-fold increase	154	138 (89.6%)	[83.7;93.9]	153	140 (91.5%)	[85.9;95.4]
Anti-IPV1	≥8 (1/dil)	159	159 (100.0%)	[97.7;100.0]	152	150 (98.7%)	[95.3;99.8]
Anti-IPV2	≥8 (1/dil)	159	159 (100.0%)	[97.7;100.0]	152	152 (100.0%)	[97.6;100.0]
Anti-IPV3	≥8 (1/dil)	159	159 (100.0%)	[97.7;100.0]	152	151 (99.3%)	[96.4;100.0]

M: number of subjects with data available

*Pertussis vaccine response is defined as:

- If pre-vaccination antibody concentration was <4*LLOQ, then the post-vaccination antibody concentration was to be ≥4*LLOQ,
- If pre-vaccination antibody concentration was ≥4*LLOQ, then the post-vaccination antibody concentration was to be ≥pre-immunisation levels.

Source: Table11.12, HXM01C CSR

Table 11. Summary of post-dose 3 GMCs or GMTs for Hexyon vaccine antigens – PPS

	Hexyon + MenC (N=162)				Hexyon (N=160)			
Component	**M**	**Geometric mean (GMC/GMT)***	**95% CI**	**Min. ; Max.**	**M**	**Geometric mean (GMC/GMT)***	**95% CI**	**Min. ; Max.**
Anti-HBs (mIU/mL)	160	242.75	[195.05;302.11]	2.50 ; 4880.00	155	267.58	[212.65;336.70]	2.50 ; 2700.00
Anti-PRP (µg/mL)	160	3.49	[2.88;4.24]	0.03 ; 119.00	158	1.89	[1.49;2.38]	0.03 ; 47.20
Anti-D (IU/mL)	160	0.08	[0.07;0.10]	0.020 ; 0.640	158	0.09	[0.08;0.10]	0.005 ; 1.280
Anti-T (IU/mL)	159	1.17	[1.07;1.29]	0.19 ; 5.65	156	0.78	[0.70;0.87]	0.08 ; 5.42
Anti-PT (EU/mL)	160	129.74	[118.93;141.52]	28.00 ; 676.00	159	139.91	[126.98;154.15]	25.00 ; 601.00
Anti-FHA (EU/mL)	158	123.54	[112.47;135.69]	18.00 ; 515.00	156	147.77	[134.82;161.97]	14.00 ; 514.00
Anti-IPV1 (1/dil)	159	92.49	[75.06;113.97]	8.00 ; 2896.30	152	126.84	[101.46;158.56]	4.00 ; 4096.00
Anti-IPV2 (1/dil)	159	90.90	[73.23;112.83]	8.00 ; 5792.60	152	104.72	[82.66;132.67]	8.00 ; 5792.60
Anti-IPV3 (1/dil)	159	173.30	[138.20;217.31]	8.00 ; 5792.60	152	250.78	[197.56;318.34]	4.00 ; 8192.00

M: number of subjects with data available

*GMCs for anti-HBs, anti-PRP, anti-D, anti-T, anti-PT and anti-FHA antibodies; GMTs for anti-IPV1, anti-IPV2 and anti-IPV3 antibodies

Source: Table11.13, HXM01C CSR

4.2.3. Discussion

Following primary vaccination with 3 doses, the HepB SBR (≥ 10mIU/mL) after Hexyon + MenC was non-inferior to that after Hexyon without MenC. Further, all subjects showed protective antibody levels against MenC at 1 month-post 2nd dose.

Data showed that the concomitant administration of Hexyon and MenC conjugate vaccine did not negatively impact the immune response to both vaccines' antigens.

Antibody levels and seroprotection /vaccine response rates obtained after co-administration of Hexyon and MenC vaccine were very similar to those after Hexyon administered without MenC. Nevertheless, with regard to diphtheria and hepatitis B, primary vaccination with Hexyon resulted in antibody concentrations providing short-term but not long-term protection. They should thus be followed up after booster vaccination.

4.3. Clinical Safety aspects

4.3.1. Methods –safety measurements

The **safety endpoints** of study were the percentages of subjects with the following adverse events:

In the 30 minutes after each vaccination:

- Any unsolicited (spontaneously reported) systemic adverse events

From Day 0 to Day 7 following each vaccination:

- Solicited injection site reactions: erythema, swelling, pain
- Solicited systemic adverse reactions: pyrexia, vomiting, crying, somnolence, anorexia, irritability

From Day 0 to Day 30 after each vaccination:

- Any unsolicited (spontaneously reported) injection site reactions and unsolicited systemic adverse events

From the time the informed consent was signed to the last visit:

- Serious adverse events (SAEs)

AEs of special interest (AESI) are AEs considered by the Sponsor to be relevant for the monitoring of the safety profile of the investigational vaccine were also reported throughout the study. AESI included extensive limb swelling (ELS), hypotonic hyporesponsive episodes (HHE), convulsions (whether febrile or not), anaphylactic reactions, apnoea, severe neurological conditions and sudden infant death syndrome (SIDS) or sudden unexpected death (SUD) (although no increased risk of SIDS/SUD has been associated with hexavalent paediatric vaccines currently on the market).

By definition, convulsions, HHE, anaphylactic reaction (including cardiac and respiratory symptoms), severe neurological conditions and fatal outcomes should be considered as serious adverse events.

Data sets analysed

The Safety Analysis Set was defined as all subjects who received at least one dose of study vaccine(s) (Hexyon and MenC) and who had safety follow-up data.

One subject randomised to the Hexyon + MenC group was not vaccinated as per randomisation and did not receive the MenC vaccine. This subject was analysed according to the vaccine actually received and was therefore accounted in the Hexyon group for the Safety Set.

Consequently, for the first vaccination, there were 174 subjects analysed for safety in the Hexyon + MenC group and 176 subjects analysed for safety in the Hexyon group.

4.3.2. Results

All subjects included in the study reported at least one adverse event (**Table 12.**).

Four subjects (1.1% of all subjects), all in the Hexyon group, experienced an immediate unsolicited AE within 30 minutes after any vaccination, 3 of which were adverse reactions.

- The 3 immediate unsolicited reactions were rash (grade 1, after 2nd dose), constipation (grade 3, 1st dose), and flatulence (grade 3, 1st dose). None of these events fulfilled seriousness criteria.
- The immediate unsolicited AE considered as not related to the study vaccines was grade 1 constipation, occurring after the first vaccination.

The frequencies of solicited injection site reactions reported within 7 days after Hexyon injection tended to be higher in the Hexyon + MenC group (85%) than in the Hexyon group (74%; **Table 13.**); injection site pain was the most frequent one, followed by erythema and swelling. Most injection site reactions were of grade 1 or 2 (see Table 12.5; CSR).

All subjects experienced at least one solicited systemic reaction within 7 days after any vaccine injection (**Table 14.**). For both groups, the most frequent solicited systemic reactions were irritability, somnolence, crying, pyrexia, and decreased appetite. No notable differences were observed between both groups, except for crying which was reported more frequently in the Hexyon + MenC group (85% versus 71% in the Hexyon group). The frequency of vomiting also tended to be higher in the Hexyon + MenC group (36% versus 27%). No notable differences were observed between the two groups regarding intensity of solicited systemic reactions which were mostly of grade 1 or 2. However, grade 3 crying tended to be reported more frequently in the Hexyon + MenC group (6% versus 2%). Two subjects from the Hexyon + MenC group experienced grade 3 pyrexia (>39.5°C). In both cases, pyrexia occurred between Day 0 and Day 3 after the 1st vaccination, lasted 1 to 2 days and resolved.

The overall frequency of unsolicited non-serious AEs occurring within 30 days after any vaccine injection was 60% in the Hexyon + MenC group and 61% in the Hexyon group (**Table 15.**). Generally, no difference was observed in the frequency of various unsolicited non-serious AEs in both groups.

Unsolicited non-serious ARs within 30 days after any vaccine injection were slightly more frequent in the Hexyon + MenC group (28% versus 23% in the Hexyon group). The most frequent unsolicited non-serious adverse reactions were injection site induration, diarrhoea, and injection site bruising. One subject in the Hexyon + MenC group and two subjects in the Hexyon group reported rash of grade 1 considered to be related to vaccination. The events of rash (mainly located on the face) occurred within 6 days after the first or second vaccination and lasted for 1 to 6 days. They all resolved without corrective treatment.

Neither AESI nor deaths were reported during the study period.

The incidence of SAEs was low in both groups: 4 subjects (2.3%) in the Hexyon + MenC group and 2 subjects (1.1%) in the Hexyon group. Only one of the 6 SAEs was considered related to the study

vaccines (pyrexia of grade 2 (leading to hospitalisation and treated with paracetamol) occurring in a subject after receiving the 1st doses of Hexyon and MenC and lasting 6 hours. The other SAEs, all considered as non-related to the study vaccines, were urinary tract infection (grade 1), gastroenteritis (grade 2), pneumonia (grade 2), pyelonephritis (grade 3) for 4 subjects, and skin neoplasm bleeding (grade 3; haemangioma bleeding leading to the subject's withdrawal after the first vaccination, see below).

Three subjects withdrew from the study after the first vaccination due to AEs, including 2 non-serious AEs considered related to the study vaccines (asthenia and crying, both of grade 3) and one SAE considered not related to the study vaccines (skin neoplasm bleeding of grade 3).

Assessor's comment:

Solicited reaction site and systemic reactions and unsolicited AEs and ARs were reported with similar frequencies in both groups although for some safety endpoints higher numbers of subjects experienced AEs following concomitant administration of Hexyon and MenC vaccine, most of grade 1 or 2.

Only one of the 6 SAEs (pyrexia of grade 2, leading to hospitalization) was related to vaccination.

Overall, no safety concerns evolved regarding co-administration of both vaccines.

Table 12. Overview of safety findings after any vaccine injection - Safety Analysis Set

	Hexyon + MenC (N=174)		Hexyon (N=176)	
Period / Subjects with at least one:	**n (%)**	**95% CI**	**n (%)**	**95% CI**
AE within 30 days after any injection:	**174 (100%)**	**[97.9;100]**	**176 (100%)**	**[97.9;100]**
Immediate unsolicited AE	0	-	4 (2.3%)	[0.6;5.7]
Immediate unsolicited AR	0	-	3 (1.7%)	[0.4;4.9]
Solicited reaction	174 (100%)	[97.9;100]	176 (100%)	[97.9;100]
Solicited injection site reaction	155 (89.1%)	[83.5;93.3]	130 (73.9%)	[66.7;80.2]
After Hexavalent vaccine	147 (84.5%)	[78.2;89.5]	130 (73.9%)	[66.7;80.2]
After MenC vaccine	124 (71.3%)	[63.9;77.9]	-	-
Solicited systemic reaction	174 (100%)	[97.9;100]	176 (100%)	[97.9;100]
Unsolicited AE	105 (60.3%)	[52.7;67.7]	109 (61.9%)	[54.3;69.1]
Unsolicited AR	47 (27.0%)	[20.6;34.3]	40 (22.7%)	[16.8;29.6]
Unsolicited non-serious AE	105 (60.3%)	[52.7;67.7]	108 (61.4%)	[53.7;68.6]
Unsolicited non-serious AR	47 (27.0%)	[20.6;34.3]	40 (22.7%)	[16.8;29.6]
Unsolicited non-serious injection site AR	28 (16.1%)	[11.0;22.4]	19 (10.8%)	[6.6;16.3]
After Hexavalent vaccine	24 (13.8%)	[9.0;19.8]	19 (10.8%)	[6.6;16.3]
After MenC vaccine	14 (8.0%)	[4.5;13.1]	-	-
Unsolicited non-serious systemic AE	100 (57.5%)	[49.8;64.9]	104 (59.1%)	[51.4;66.4]
Unsolicited non-serious systemic AR	26 (14.9%)	[10.0;21.1]	28 (15.9%)	[10.8;22.2]
AE leading to study discontinuation	1 (0.6%)	[<0.1;3.2]	2 (1.1%)	[0.1;4.0]
AR leading to study discontinuation	1 (0.6%)	[<0.1;3.2]	1 (0.6%)	[<0.1;3.1]
SAE	4 (2.3%)	[0.6;5.8]	2 (1.1%)	[0.1;4.0]
SAR	1 (0.6%)	[<0.1;3.2]	0	-
Death	0	-	0	-
SAE leading to study discontinuation	0	-	1 (0.6%)	[<0.1;3.1]
SAR leading to study discontinuation	0	-	0	-
AE during the study	**174 (100%)**	**[97.9;100]**	**176 (100%)**	**[97.9;100]**
SAE	4 (2.3%)	[0.6;5.8]	2 (1.1%)	[0.1;4.0]
Death	0	-	0	-

n: number of subjects experiencing the endpoint listed in the first column; AE: adverse event; AR: adverse reaction. 95% CI: The two-sided 95% CI of the percentage of subjects presenting at least once the considered event is calculated using the exact binomial method. Source: CSR of Study HXM01C, Table 12.2

Table 13. Solicited injection site reactions within 7 days after any vaccine injection – Safety Analysis Set

	Hexyon + MenC (N=174)		Hexyon (N=176)	
Subjects with at least one:	n (%)	95% CI	n (%)	95% CI
Solicited injection site reaction:	**155 (89.1%)**	**[83.5;93.3]**	**130 (73.9%)**	**[66.7;80.2]**
Injection site erythema	110 (63.2%)	[55.6;70.4]	97 (55.1%)	[47.4;62.6]
Injection site pain	128 (73.6%)	[66.4;79.9]	109 (61.9%)	[54.3;69.1]
Injection site swelling	69 (39.7%)	[32.3;47.3]	61 (34.7%)	[27.7;42.2]
After Hexavalent vaccine	147 (84.5%)	[78.2;89.5]	130 (73.9%)	[66.7;80.2]
Injection site erythema	95 (54.6%)	[46.9;62.1]	97 (55.1%)	[47.4;62.6]
Injection site pain	120 (69.0%)	[61.5;75.7]	109 (61.9%)	[54.3;69.1]
Injection site swelling	60 (34.5%)	[27.5;42.1]	61 (34.7%)	[27.7;42.2]
After MenC vaccine	124 (71.3%)	[63.9;77.9]	-	-
Injection site erythema	78 (44.8%)	[37.3;52.5]	-	-
Injection site pain	106 (60.9%)	[53.2;68.2]	-	-
Injection site swelling	45 (25.9%)	[19.5;33.0]	-	-

n: number of subjects experiencing the endpoint listed in the first column
95% CI: The two-sided 95% CI of the percentage of subjects presenting at least once the considered event is calculated using the exact binomial method. Source: CSR of Study HXM01C, Table 12.4

Table 14. Solicited Systemic Reactions within 7 days After any Vaccine Injection – Safety Analysis Set

	Hexyon + MenC (N=174)		Hexyon (N=176)	
Subjects with at least one:	**n (%)**	**95% CI**	**n (%)**	**95% CI**
Solicited systemic reaction	174 (100%)	[97.9;100]	176 (100%)	[97.9;100]
Crying	148 (85.1%)	[78.9;90.0]	125 (71.0%)	[63.7;77.6]
Decreased appetite	98 (56.3%)	[48.6;63.8]	96 (54.5%)	[46.9;62.1]
Irritability	166 (95.4%)	[91.1;98.0]	166 (94.3%)	[89.8;97.2]
Pyrexia	126 (72.4%)	[65.1;78.9]	127 (72.2%)	[64.9;78.6]
Somnolence	144 (82.8%)	[76.3;88.1]	151 (85.8%)	[79.7;90.6]
Vomiting	63 (36.2%)	[29.1;43.8]	47 (26.7%)	[20.3;33.9]

n: number of subjects experiencing the endpoint listed in the first column
95% CI: The two-sided 95% CI of the percentage of subjects presenting at least once the considered event is calculated using the exact binomial method. Source: CSR of Study HXM01C, Table 12.6

Table 15. Most Frequent Unsolicited Non-Serious Adverse Events within 30 days after any vaccine injection - Safety Analysis Set

	Hexyon + MenC (N=174)			Hexyon (N=176)		
Subjects with at least one:	**nAEs**	**n (%)**	**95% CI**	**nAEs**	**n (%)**	**95% CI**
Unsolicited non-serious AE	**248**	**105 (60.3%)**	**[52.7;67.7]**	**215**	**108 (61.4%)**	**[53.7;68.6]**
Gastrointestinal disorders	55	37 (21.3%)	[15.4;28.1]	57	40 (22.7%)	[16.8;29.6]
Diarrhoea	17	14 (8.0%)	[4.5;13.1]	15	12 (6.8%)	[3.6;11.6]
Flatulence	7	7 (4.0%)	[1.6;8.1]	12	9 (5.1%)	[2.4;9.5]
Teething	12	9 (5.2%)	[2.4;9.6]	5	5 (2.8%)	[0.9;6.5]
General disorders and administration site conditions	66	40 (23.0%)	[17.0;30.0]	40	34 (19.3%)	[13.8;25.9]
Injection site bruising	11	9 (5.2%)	[2.4;9.6]	7	7 (4.0%)	[1.6;8.0]
Injection site induration	25	14 (8.0%)	[4.5;13.1]	10	9 (5.1%)	[2.4;9.5]
Pyrexia	6	5 (2.9%)	[0.9;6.6]	11	10 (5.7%)	[2.8;10.2]
Infections and infestations	90	62 (35.6%)	[28.5;43.2]	81	62 (35.2%)	[28.2;42.8]
Rhinitis	34	24 (13.8%)	[9.0;19.8]	32	26 (14.8%)	[9.9;20.9]
Upper respiratory tract infection	29	25 (14.4%)	[9.5;20.5]	27	27 (15.3%)	[10.4;21.5]
Respiratory, thoracic and mediastinal disorders	15	12 (6.9%)	[3.6;11.7]	11	11 (6.3%)	[3.2;10.9]
Cough	12	9 (5.2%)	[2.4;9.6]	9	9 (5.1%)	[2.4;9.5]

*System organ classes are presented in this table if they include at least one preferred term reported with a frequency
>5%.
n: number of subjects experiencing the endpoint listed in the first column; nAEs: number of AEs
95% CI: The two-sided 95% CI of the percentage of subjects presenting at least once the considered event is calculated using the exact binomial method. Source: CSR of Study HXM01C, Table 12.9

4.3.3. Discussion

The safety profile of Hexyon/Hexacima was generally similar whether co-administered or not with a meningococcal serogroup C conjugate vaccine and is consistent with the one previously described in clinical trials.

The immunogenicity and safety findings of this study support the concomitant administration of Hexyon/Hexacima with a meningococcal serogroup C conjugate vaccine.

4.4. Changes to the Product Information

As a result of this variation, section(s) 4.5 and 5.1 of the SmPC are being updated (additions in **bold** deletions ~~strikethrough~~). The Package Leaflet (PL) is updated accordingly.

SmPC

4.5 Interaction with other medicinal products and other forms of interaction

Data on concomitant administration of Hexacima with a pneumococcal polysaccharide conjugate vaccine have shown no clinically relevant interference in the antibody response to each of the antigens.

Data on concomitant administration of a booster dose of Hexacima with measles-mumps-rubella vaccines have shown no clinically relevant interference in the antibody response to each of the antigens. There

may be a clinically relevant interference in the antibody response of Hexacima and a varicella vaccine and these vaccines should not be administered at the same time.

Data on concomitant administration of rotavirus vaccines have shown no clinically relevant interference in the antibody response to each of the antigens.

Data on concomitant administration of Hexacima with a meningococcal C conjugate vaccine have shown no clinically relevant interference in the antibody response to each of the antigens.
~~No data are available on concomitant administration of Hexacima with meningococcal vaccines.~~

If co-administration with another vaccine is considered, immunisation should be carried out on separate injections sites.

Hexacima must not be mixed with any other vaccines or other parenterally administered medicinal products.

~~Except in the case of immunosuppressive therapy (see section 4.4), n~~ No significant clinical interaction with other treatments or biological products has been reported **except in the case of immunosuppressive therapy (see section 4.4).**

Interference with laboratory testing: see section 4.4.

5.1 Pharmacodynamic properties

Table 1: Percentage of individuals with antibody titres ≥ seroprotection / seroconversion rates* one month after a 3 doses primary vaccination with Hexacima

Antibody titres ≥ seroprotection / seroconversion rates		**6-10-14 Weeks† N††=123 to 220**	**2-3-4 Months† N††=~~145~~322**	**2-4-6 Months† N††=934 to 1270**
		%	**%**	**%**
Anti-diphtheria (≥ 0.01 IU/ml)		97.6	~~99.3~~**99.7**	97.1
Anti-tetanus (≥ 0.01 IU/ml)		100.0	100.0	100.0
Anti-PT **(Vaccine response§)**~~(≥ 4 fold rise)~~		~~93.6~~**100.0**	~~93.6~~**99.4**	~~96.0~~**99.7**
Anti-FHA **(Vaccine response§)**~~(≥ 4 fold rise)~~		~~93.1~~**100.0**	~~81.9~~**99.7**	~~97.0~~**99.9**
Anti-HBs (≥ 10 mIU/ml)	With hepatitis B vaccination at birth	99.0	/	99.7
	Without hepatitis B vaccination at birth	95.7	~~94.0~~**96.8**	98.8
Anti-Polio type 1 (≥ 8 (1/dilution))		100.0	~~97.7~~**99.4**	99.9
Anti-Polio type 2 (≥ 8 (1/dilution))		98.5	~~94.7~~**100.0**	100.0
Anti-Polio type 3 (≥ 8 (1/dilution))		100.0	~~97.4~~**99.7**	99.9
Anti-PRP (≥ 0.15 µg/ml)		95.4	~~90.7~~**96.2**	98.0

* Acceptable as correlates or surrogates of protection

† 6, 10, 14 weeks with and without hepatitis B vaccination at birth (Republic of South Africa); 2, 3, 4 months without hepatitis B vaccination at birth (~~Turkey~~ Finland); 2, 4, 6 months without hepatitis B vaccination at birth (Argentina, Mexico, Peru); 2, 4, 6 months with hepatitis B vaccination at birth (Costa Rica and Colombia)

†† Number of individuals analysed (per protocol set)

§Vaccine response: If pre-vaccination antibody concentration <8 EU / mL, then the post-vaccination antibody concentration should be ≥ 8 EU / mL. Otherwise, post-vaccination antibody concentration should be ≥ pre-immunisation level.

Package Leaflet

Other medicines or vaccines and Hexacima

Tell your doctor or nurse if your child is taking, has recently taken or might take any other medicines or vaccines.
Hexacima can be given at the same time as other vaccines such as pneumococcal vaccines, measles-mumps-rubella vaccines, ~~or~~ rotavirus vaccines **or meningococcal vaccines**.
When given at the same time with other vaccines, Hexacima will be given at different injection sites.

5. Request for supplementary information

5.1. Other concerns

Clinical aspects:

Regarding Hexyon/Hexacima/Hexaxim SmPC:

Table 1 (SmPC section 5.1) should be updated as follows

- keep the pertussis data of 4-fold rise but use term 'seroconversion rate' instead of >4-fold rise (in order to match this with title wording) – otherwise exchange 'seroconversion rate' in title by 'vaccine response'
- present pertussis data as both, vaccine response and seroconversion rate
- The explanation for calculation of seroconversion (i.e., minimum 4-fold increase compared to pre-vaccination level) should be added as a table footnote.

Further, pertussis data of Table 2 should be updated accordingly.

Additional note to the applicant:

Following completion of WS 676 (linguistic check) the assessor stumbled over a typing mistake in the SmPC, Table 2: vaccine response in the footnote was described as '*Post-booster antibody concentration ≥4-fold rise if pre-booster antibody concentration <8 EU/ml. Post-booster antibody concentration ≥2-fold rise if pre-booster antibody concentration ≥8 EU/ml'* which is actually the description of booster response. This should be corrected.

This mixing up should be reconsidered during the preparation of responses.

Additional comment of the assessor:

To provide the **most useful** information to the prescriber/health care professionals, the assessor suggests to present aP data

- In table 1 (primary vaccination) as **vaccine response** and seroconversion rate (≥ 4fold rise relative to pre-vaccination);
- In table 2 (booster vaccination) as **booster response** and seroconversion rate (≥ 4fold rise relative to pre-vaccination);

and include respective table footnotes to describe seroconversion rate and vaccine response or booster response, respectively.

In order to allow the regulatory authorities of the other EU member states to evaluate the changes it is important to integrate changes of both WS676 and 702 within the responses to RSI (WS702).

Please note that changes to Table 2 made in WS676 cannot be seen in the SmPC submitted with WS702 as the latter contains the previous SmPC version (before adoption of WS676).

6. Assessment of the responses to the 1st request for supplementary information

6.1. Other concerns

Clinical aspects: Question regarding corrections of SmPC

Summary of the WSA's response

The applicant has updated the SmPC for Hexacima with acellular pertussis (PT, FHA) immunogenicity data. Changes adopted following the previous WS 676 were integrated in the submitted SmPC in order to demonstrate concordant update of Table 1 (primary vaccination) and Table 2 (booster vaccination) of SmPC Section 5.1.

Assessment of the WSA's response

The changes are generally endorsed. However, in Table 2 aP data still need to be further updated/ commented – please see 2nd request for supplementary information.

7. 2nd Request for supplementary information

7.1. Other concerns

Clinical aspects:

1. The inconsistency in calculation of 'seroconversion', i.e. >4-fold increase compared to pre-vaccination level (2+1 schedule) and >4-fold increase compared to pre-booster level (3+1 schedule), is not acceptable. The applicant is asked to consistently calculate seroconversion as >4-fold increase compared to pre-vaccination level.

2. The applicant is asked to comment on how calculation of booster response data was performed. In a previous submission the same data were described as 'vaccine response'.

3. Further, the table footnote should be further adapted by exchanging the term 'generally accepted correlates or surrogates of protection' by 'generally accepted surrogates (PT, FHA) or correlates of protection (other components)'. (Please also refer to attached SmPC document, p. 10 and p 22).

8. Assessment of the responses to the 2nd request for supplementary information

8.1. Other concerns:

Clinical aspects: Questions regarding SmPC update

Question 1

The inconsistency in calculation of 'seroconversion', i.e. >4-fold increase compared to pre-vaccination level (2+1 schedule) and >4-fold increase compared to pre-booster level (3+1 schedule), is not acceptable. The applicant is asked to consistently calculate seroconversion as >4-fold increase compared to pre-vaccination level.

Summary of the WSA's response

The Applicant understands and acknowledges the Rapporteur's comment on a clarification of the calculation of 'seroconversion'.

The applicant agrees to consistently calculate seroconversion as >=4-fold increase compared to pre-vaccination (pre-dose 1) level for 3+1 and 2+1 schedules.

By consequence the seroconversion rates after booster vaccination were calculated for the 3+1 schedules and are presented in Appendix 1 for the following studies:

- A3L15: booster dose at 15-18 Months of Age (MoA) after a 3-dose primary immunization at 6, 10 and 14 weeks of age;
- A3L22: booster dose at 15-18 MoA after a 3-dose primary immunization at 2, 3 and 4 MoA in A3L10;
- A3L21: booster dose at 15-18 MoA after a 3-dose primary immunization at 2, 4 and 6 MoA in A3L11.

The seroconversion rates for the 2+1 schedule were already calculated as defined above and were presented in table 5.2 of the CSR of A3L38 study page 108-109 and tables 4.4 and 4.5 page 21-22 of A3L38 addendum of module 2.5 (Ref WS676). These values were included in the Product Information Table 2 Seroprotection/ Seroconversion rates* one month after booster vaccination with Hexaxim/Hexacima/Hexyon of the section 5.1 of the Summary of Product Characteristics (SmPC) at the time of the first answer to questions on March 4th 2015.

The seroconversion values presented in the SmPC (1.3.1 Product Information) section 5.1 Table 2 have been revised accordingly.

The proposed footnote corresponding to the seroconversion is as follows:

"‡‡ Seroconversion: minimum 4-fold increase compared to pre-vaccination level (pre-dose 1)"

Assessor's comment:

The MAH/SOH has updated the seroconversion rates for aP components in table 1 and 2 of SmPC section 5.1 to consistently express ≥ 4-fold increase compared to pre-dose 1 for both 2+1 and 3+1 vaccination schedules.

The changes are acknowledged and approved.

Question 2

The applicant is asked to comment on how calculation of booster response data was performed. In a previous submission the same data were described as 'vaccine response'.

Summary of the WSA's response

The Applicant understands and acknowledges the Rapporteur's comment on a clarification of the calculation of 'Booster response' compared to the calculation of 'Vaccine response' in Table 2 Seroprotection/Sero- conversion rates* one month after booster vaccination with Hexaxim/Hexacima/Hexyon of the section 5.1 of the SmPC.

The applicant recognizes that the terminology "Vaccine response" as presented initially in the Table 2 of the SmPC of variation A3L38 (Ref WS676) was confusing. It should have been called "Booster Response" as defined below and in accordance with the A3L38 CSR:

Post-booster antibody concentration ≥4-fold rise if pre-booster antibody concentration <8 EU/ml; or post-booster antibody concentration ≥2-fold rise if pre-booster antibody concentration ≥8 EU/ml

During the assessment of the HXM01C variation (Ref WS702) the Rapporteur pointed out the discrepancies between "Vaccine response" terminology and the data presented corresponding to "Booster response". Consequently the applicant changed the terminology in the Table 2 from "Vaccine response" to "Booster response" in the first answers to questions on March 4th 2015.

As requested by the Rapporteur to present the seroconversion referring to pre-vaccination level (pre-dose 1), and, for ease of understanding, the applicant proposes to have a similar approach for presenting pertussis response rates in Table 2 and to refer to pre-vaccination level (pre-dose 1) instead of pre-booster level.

To that respect the Vaccine response is presented in the Table 2 and defined as:

Vaccine response: If pre-vaccination antibody concentration (pre-dose 1) <8 EU/ml, then the post-booster antibody concentration should be >=8 EU/ml. Otherwise, post-booster antibody concentration should be >= pre-immunisation level (pre-dose 1).

For the purpose of the Applicant response, vaccine responses after booster dose administration were calculated for 3+1 schedules and are presented in Appendix 1 for the following studies:

- A3L15: booster dose at 15-18 Months of Age (MoA) after a 3-dose primary immunization at 6, 10 and 14 weeks of age;
- A3L22: booster dose at 15-18 MoA after a 3-dose primary immunization at 2, 3 and 4 MoA in

A3L10;

- A3L21: booster dose at 15-18 MoA after a 3-dose primary immunization at 2, 4 and 6 MoA in A3L11.

The vaccine response for the 2+1 schedule were already calculated as defined above and were presented in table 5.1 of the CSR of A3L38 study page 105 and table 4.1 page 18 of A3L38 addendum of module 2.5 (Ref WS676).

The vaccine responses values presented in the Summary of Product Characteristics (1.3.1 Product Information) section 5.1 Table 2 have been revised accordingly.

The proposed footnote corresponding to the vaccine response is as follows:

"§Vaccine response: If pre-vaccination antibody concentration (pre-dose 1) <8 EU/ml, then the post-booster antibody concentration should be ≥8 EU/ml. Otherwise, post-booster antibody concentration should be ≥ pre-immunisation level (pre-dose 1)."

Assessor's comment:

The MAH/SOH has clarified discrepancies between vaccine response/ booster response terminology and respective aP data. In addition, for 'ease of understanding' the MAH/SOH exchanged booster response data in table 2 of SmPC section 5.1 by vaccine response data (presented in Appendix 1). Although booster response data would be more appropriate for the booster dose, the use of 'vaccine response' data is acknowledged as it is consistent with those in table 1 and thus facilitates readability of SmPC.

The changes are accepted

Question 3

Further, the table footnote should be further adapted by exchanging the term 'generally accepted correlates or surrogates of protection' by 'generally accepted surrogates (PT, FHA) or correlates of protection (other components)'.

Summary of the WSA's response

The Applicant acknowledges the Rapporteur's comment on an adaptation of the footnote in the Table 1 and 2 of section 5.1 of the SmPC.

The term 'generally accepted correlates or surrogates of protection' was replaced by 'generally accepted surrogates (PT, FHA) or correlates of protection (other components)' each time the requested change applies.

The footnotes presented in the Summary of Product Characteristics (1.3.1 Product Information) section 5.1 Table 1 and Table 2 have been revised accordingly.

Assessor's comment:

The MAH/SOH has updated the table footnotes as suggested beforehand. The changes are approved.

Appendix 1 of the applicant's responses to questions

Seroconversion and Vaccine Response Rates One Month after Booster Vaccination

Table 1: Anti-PT Antigen: Seroconversion and vaccine response rates one month after booster vaccination

Schedule	Trial	Criteria	Post Booster vaccination		
			M	%	(95% CI)
6, 10, 14 Weeks//15-18 Months	A3L15 (1*)	Seroconversion†	160	94.4	(89.6; 97.4)
		Vaccine response‡	160	100	(97.7; 100)
2, 3, 4//15-18 Months	A3L10/A3L22	Seroconversion	107	96.3	(90.7; 99.0)
		Vaccine response	107	100	(96.6; 100)
2, 4, 6//15-18 Months	A3L11§/A3L21	Seroconversion	130	96.2	(91.3; 98.7)
		Vaccine response	130	100	(97.2; 100)

M: number of subjects available for the endpoint from the per protocol analysis set

%: percentages and 95% CI are calculated according to the subjects available for the endpoint

**: Hexaxim without hepatitis b at birth*

†: Seroconversion: minimum 4-fold increase compared to pre-vaccination level (pre-dose 1)

‡: Vaccine response: If pre-vaccination antibody concentration (pre-dose 1) <8 EU/ml, then the post-booster antibody concentration should be ≥8 EU/ml. Otherwise, post-booster antibody concentration should be ≥ pre-immunisation level (pre-dose 1)

§: For A3L11, the 3 lots pooled of Hexaxim are presented

Note: For A3L21 and A3L22 post-booster results correspond to all subjects primed with Hexaxim and boosted with Hexaxim

Study: 352 - Hexaxim Program: Add_Immuno_Table 1_2 Datasets: ADIM ADSL Output: IM_001.RTF DATE: 31MAR2015 20:06

Table 2: Anti-FHA Antigen: Seroconversion and vaccine response rates one month after booster vaccination

Schedule	Trial	Criteria	Post Booster vaccination		
			M	%	(95% CI)
6, 10, 14 Weeks//15-18 Months	A3L15 (1*)	Seroconversion†	158	99.4	(96.5; 100)
		Vaccine response‡	158	100	(97.7; 100)
2, 3, 4//15-18 Months	A3L10/A3L22	Seroconversion	107	94.4	(88.2; 97.9)
		Vaccine response	107	98.1	(93.4; 99.8)
2, 4, 6//15-18 Months	A3L11§/A3L21	Seroconversion	129	98.4	(94.5; 99.8)
		Vaccine response	129	100	(97.2; 100)

M: number of subjects available for the endpoint from the per protocol analysis set

%: percentages and 95% CI are calculated according to the subjects available for the endpoint

**: Hexaxim without hepatitis b at birth*

†: Seroconversion: minimum 4-fold increase compared to pre-vaccination level (pre-dose 1)

‡: Vaccine response: If pre-vaccination antibody concentration (pre-dose 1) <8 EU/ml, then the post-booster antibody concentration should be ≥8 EU/ml. Otherwise, post-booster antibody concentration should be ≥ pre-immunisation level (pre-dose 1)

§: For A3L11, the 3 lots pooled of Hexaxim are presented

Note: For A3L21 and A3L22 post-booster results correspond to all subjects primed with Hexaxim and boosted with Hexaxim

Study: 352 - Hexaxim Program: Add_Immuno_Table 1_2 Datasets: ADIM ADSL Output: IM_002.RTF DATE: 31MAR2015 20:06

Table 3: Anti-PT and anti-FHA A3L38 summary results: Seroconversion and vaccine response rates (Per Protocol Analysis Set 1)

			DTaP-IPV-HB-Hib + Prevenar 13 (N=249)		
Component	**Timepoint**	**Criteria**	**n/M**	**%**	**(95% CI)**
Anti- PT (ELISA - EU/mL	**Post-Dose 3/ Pre-Dose 1**	**Seroconversion***	231/245	94.3	(90.6; 96.8)
		Vaccine response†	240/245	98.0	(95.3; 99.3)
Anti- FHA (ELISA - EU/mL	**Post-Dose 3/ Pre-Dose 1**	**Seroconversion***	241/247	97.6	(94.8; 99.1)
		Vaccine response†	247/247	100.0	(98.5; 100.0)

Source: A3L38 CSR, Table 5.1 and Table 5.2

N: Number of subjects analyzed according to the PP1; n: number of subjects; M: number of subjects available for the endpoint

%: percentages and 95% CIs were calculated according to the subjects available for the endpoint

** Seroconversion: minimum 4-fold increase compared to pre-vaccination level (pre-dose 1)*

† Vaccine response: If pre-vaccination antibody concentration (pre-dose 1) <8 EU/ml, then the post-Dose 3 antibody concentration should be ≥8 EU/ml. Otherwise, post-Dose 3 antibody concentration should be ≥ pre-immunisation level (pre-dose 1).

Conclusion

☒ No need to update overall conclusion and impact on benefit-risk balance