Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Mutual Recognition Procedure

Menitorix
0.5 ml single dose

Haemophilus type b and *Meningococcal* group C conjugate vaccine

UK/H/0954/001/MR

UK licence no: PL 10592/0217

SMITHKLINE BEECHAM LIMITED

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for Menitorix a 0.5 ml single dose vaccine (PL 10592/0217; UK/H/0954/001/MR). This report will refer to Menitorix 0.5 ml single dose vaccine, as Menitorix, from this instance onward. It explains how Menitorix was assessed and explains why an authorisation was recommended, as well stating the conditions for its use. It is not intended to provide practical advice on how to use these products.

For practical information about using Menitorix, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Menitorix and what is it used for?
Menitorix is a vaccine to help prevent infectious diseases caused by *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* group C (MenC) bacteria. Hib and MenC infections are serious, potentially fatal and they can both cause meningitis (inflammation of the coverings of the brain and spinal cord) and septicaemia (blood poisoning). Menitorix is used in children after the age of 2 months up to 2 years. After the first course of vaccinations against Hib and MenC has been completed, a booster dose of Hib and MenC should be given, usually at some time in the second year of life.

Menitorix is only administered by doctors or nurses who are qualified to give vaccinations. The vaccine is injected into the muscle (usually into the thigh muscle but in toddlers the deltoid region or upper arm muscle can be used).

Menitorix is not used if the child previously had a reaction to Menitorix, to any Hib or MenC vaccine, to tetanus toxoid or any other ingredients of this medicine.

One dose (0.5 mL) of Menitorix consists of 5 µg of the purified *H. influenzae* type b capsular polysaccharide, polyribosylribitol phosphate (PRP) and 5 µg of the meningococcal polysaccharide C (PSC) both directly conjugated to tetanus toxoid (TT) carrier protein. The product is not adjuvanted, and contains no preservative.
The product is supplied as a pack of either 1 or 10 vials of Menitorix packaged together with an equal number of pre-filled syringes of solvent (0.5ml) with or without separate needles.

How does Menitorix work?
Menitorix contains components of Haemophilus type b (Hib) and *Neisseria meningitidis* group C (MenC), these components called antigens trigger an immune response, which means that the immune system should be better prepared to fight the infection the next time the person encounters either of these bacteria.

Vaccination is the best way to protect against diseases caused by these bacteria. Despite this, no vaccine can provide complete, life-long protection in all people vaccinated. Also, Menitorix can only protect against meningitis and other infections caused by *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* group C (MenC). It cannot protect against meningitis caused by other bacteria or viruses, including other types and groups of Haemophilus or Neisseria bacteria.

Rates of Hib and MenC disease in the UK are now at their lowest-ever levels as a result of vaccination.

How is Menitorix used?

Menitorix should be used in accordance with official recommendations, in the form of vaccination schedules. The vaccination schedules are included in section 4.2 of the summary of product characteristics.

The vaccination will be given by a trained healthcare professional (a doctor, or nurse). The needle will be placed into the muscle, most often of the thigh, although the upper arm can be used in children aged 12 to 24 months of age. The needle should never be placed into the blood vessels, or into the layers of skin.

What benefits of Menitorix have been shown in studies?

Formal studies of efficacy have not been performed since these would not be feasible. The measure of efficacy is instead based upon immunogenicity testing, the ability of a vaccine to provoke an immune response. The immunogenicity data indicates that Menitorix will be at least as effective as the similar licensed PRP-T and MenC conjugate vaccines when used for priming and/or for boosting in accordance with the Summary of Product Characteristics (SmPC).

The safety of Menitorix was supported by data from approximately 0.6 million toddlers who were given the vaccine as booster dose for Hib and MenC in the UK.

What are the possible side effects of Menitorix?

Very common side effects include decreased appetite, irritability, drowsiness, fever and injection site reactions (swelling, pain, redness); common side effects include injection site reactions (induration and nodule formation).

For information about side effects that may occur with using Menitorix, please refer to the PIL or the Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

Why is Menitorix approved?

Greece, Poland and Spain raised objections to the granting of the authorisation. Belgium and Ireland were in agreement. As the countries could not reach agreement, a procedure was triggered for the Commission for Human Medicinal Products to review the evidence. The committee concluded that Menitorix had been shown to have a positive benefit/risk and could be approved for use.

What measures are being taken to ensure the safe and effective use of Menitorix?

A Risk Management Plan (RMP) has been developed to ensure that Menitorix is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL for these products, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Menitorix

A marketing authorisation was granted in the UK on 19th December 2005 (PL 10592/0217).

Following a mutual recognition procedure (UK/H/0954/001/MR), Belgium, Greece, Spain, Poland and Republic of Ireland agreed to grant marketing authorisations for Menitorix on 12th November 2007.

The full PAR for Menitorix follows this summary. The scientific discussion of the PAR i.e. sections I-IV, reflect the most recent full assessment of the Marketing Authorisation for Menitorix as per procedure UK/H/0954/001/MR which concluded 12 November 2007. The PIL and SmPC on the MHRA website should be referred to for the most recently approved product information.

For more information about treatment with Menitorix, read the PIL or contact your doctor or pharmacist.

This summary was last updated in March 2016.

The information in the PAR reflects the most recent full assessment of the Marketing Authorisation for Menitorix as per procedure UK/H/0954/001/MR which concluded 12 November 2007. The PIL and SmPC on the MHRA website should be referred to for the most recently approved product information.

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I INTRODUCTION

This is an application made under Article 8.3 (i) of Directive 2003/83 for a new active substance and a known active substance, Haemophilus type b and Meningococcal group C conjugate vaccine (Menitorix 0.5ml single dose).
Menitorix is indicated for the prevention of invasive diseases caused by *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* serogroup C (MenC) in children from the age of two months.

H. influenzae is a Gram-negative coccobacillus. Prior to introduction of Meningitis conjugated vaccines, meningitis was the most common manifestation of Hib disease and accounted for 50% to 65% of all cases of invasive infections due to the organism in developed countries. The peak age incidence of Hib meningitis was around 9 months in NW Europe. Epiglottitis was the second most common manifestation of Hib disease in NW Europe with a peak age incidence somewhere between 15-24 months. Epiglottitis is regarded as a medical emergency, as a swollen epiglottis can restrict the oxygen supply to the lungs.

N. meningitidis, is a Gram-negative diplococcus. Meningoccocal meningitis is the most common clinical presentation of invasive infection. Meningococcal septicaemia, occurring with or without meningitis, has a high mortality rate even when treated promptly. Unlike Hib infections, the risk of meningococcal disease is lifelong although there are peaks in incidence at the extremes of life. The geographical distributions of invasive infections in man due to specific serogroups A, B, C, W135 and Y are variable and have important implications for implementation of vaccination programmes. As yet there is no vaccine against serogroup B. Unconjugated and conjugated vaccines against A, C, W135 and Y have been developed and licensed in various parts of the world.

This vaccine is only available by prescription with the recommended posology as follows:

Primary vaccination in infants from 6 weeks up to 12 months of age:
Three doses, each of 0.5 mL, should be given with an interval of at least 1 month between doses.

Booster vaccination of children primed in infancy with Hib and MenC conjugate vaccines:

After primary vaccination against Hib and MenC in infancy, a booster dose is recommended to ensure long-term protection. A single (0.5 mL) dose of Menitorix may be used to boost immunity to Hib and MenC in children who have previously completed a primary immunisation series with Menitorix or with other Hib or MenC conjugate vaccines. Immune responses to a booster dose of Menitorix may vary according to the vaccine used for the primary series. The timing of the booster dose of Menitorix should be in accordance with available official recommendations and would usually be given from the age of 12 months onwards, at least 6 months after the last priming dose, and before the age of 2 years.

Vaccination of children primed in infancy with Hib but not with MenC conjugate vaccines:
A single (0.5 mL) dose of Menitorix may be used to elicit immunity against MenC and to boost immunity to Hib. The timing of the vaccination with Menitorix should be in accordance with available official recommendations and should usually be from the age of 12 months onwards and before the age of 2 years. The need for booster doses in subjects primed with a single dose of MenC conjugate (i.e. aged 12 months or more when first immunised)

has not been established.

Menitorix is for intramuscular injection only, preferably in the anterolateral thigh region. In children 12 to 24 months of age, the vaccine may be administered in the deltoid region.

Menitorix should under no circumstances be administered intravascularly or intradermally.

The PRP polysaccharide in Menitorix is the same as is used in Hiberix™ (10 µg of PRP/dose) but contains only 5 µg of the PRP, which also uses TT as the carrier protein. The purified meningococcal polysaccharide C in Menitorix is produced according to the same principles that are applied for Mencevax™ AC, Mencevax ACW135 and Mencevax ACW135Y. The PRP conjugate (PRP-T) in Menitorix is the same (polysaccharide and carrier) as that used in Quintanrix™ but Quintanrix contains only 2.5 µg of the saccharide.

The vaccine is a freeze-dried preparation consisting of 5 µg of the purified *H. influenzae* type b capsular polysaccharide, polyribosylribitol phosphate (PRP) and 5 µg of the meningococcal capsular polysaccharide of serogroup C (PSC) both directly conjugated to tetanus toxoid (TT) carrier protein using a new coupling technology.

The product is supplied as a pack of either 1 or 10 vials of Menitorix packaged together with an equal number of pre-filled syringes of solvent (0.5ml) with or without separate needles. Prior to administration, Menitorix must be reconstituted with the liquid saline diluent.

No specific non-clinical studies were performed with the Hib-MenC vaccine.

Clinical studies on Menitorix were carried out in accordance with Good Clinical Practice (GCP).

Formal studies of efficacy have not been performed since these would not be feasible. The demonstration of likely efficacy rests on the immunogenicity data assessed against the postulated serological correlates of protection.

Although this application concerns the use of Hib-MenC 5/5 µg vaccine, data are also provided from investigations with a Hib-MenC 10/10 µg vaccine and experimental vaccines that contained various quantities of Hib, MenC and the meningococcal polysaccharide Y conjugated to tetanus toxoid (TT).

Because of the complex and evolving nature of the development programme that led up to this application, various formulations of the Hib-MenC 5/5 saccharide content vaccine have been assessed. Clinical data generated with the final chosen formulation (Third series lots) for the market came from the primary series study Hib-MenC-TT-012 and the booster study Hib-MenC-TT-011.

Overall the immunogenicity and safety data were considered to be satisfactory. However, it is clear that long-term follow-up of immunogenicity and effectiveness will be very important. In this light, the following studies are ongoing:

- Hib-MenC-TT-013 is the ongoing extension of study 012, described in III.2.
- Hib-MenC-TT-014 is an ongoing study in Italy and Finland in which two doses of Menitorix are administered at 3 and 5 months with Infanrix penta and compared to NeisVac-C plus Infanrix hexa.
- Hib-MenC-TT-15 is the booster dose extension of 014 as above.

o Hib-MenC-TT-016 is an ongoing study in which Menitorix is being used to boost Australian toddlers already primed with the nationally recommended vaccines and schedule.
o Hib-MenC-TT-022 is the long-term follow-up of antibody persistence in children enrolled into studies 097 and 010.
o Hib-MenC-TT-017-021 will follow-up children enrolled into 016 as above.

o Menitorix is also being used in one arm of a primary series study with the applicant's candidate pneumococcal vaccine (10 Pn-PD-DiT-011).

The quality, non-clinical and clinical expert reports have been written by appropriately qualified experts.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

This product was approved in the UK on 19th December 2005 (PL 10592/0217). This was subsequently followed by a mutual recognition procedure (UK/H/0954/001/MR) The Reference Member State was the United Kingdom and the Concerned Member States were Belgium, Greece, Ireland, Poland and Spain. These Member States were not able to reach an agreement in respect of the Mutual Recognition of the Marketing Authorisation at the end of procedure. The United Kingdom referred the reasons for disagreement to the Co-ordination group for Mutual recognition and Decentralised procedures (CMDh) in January 2007 no agreement was reached. Therefore, a referral to the Committee for Human Medicinal Products (CHMP) was initiated on 29 March 2007.

Public health objections were raised because no immunological correlates of protection were established for MenC conjugates and because the submission of data on pre-licensure effectiveness was required to cover infant and toddler use. Furthermore, it could not be accepted that no data on the use of Menitorix or on antibody persistence beyond the second year of life was provided. These objections were considered to be of serious public health concern.

During their November 2007 meeting, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, was of the opinion that the benefit/risk ratio is favourable for Menitorix, that the objections raised by Greece, Poland and Spain should not prevent the granting of a Marketing Authorisation and that the Summary of Product Characteristics, labelling and package leaflet of the Reference Member State should be amended. A positive opinion was adopted by consensus on 15 November 2007.

All commitments made at the time of the initial MAA have been fulfilled. Clinical studies were continued, finalized and submitted as a commitment, a submission in accordance with Article 46 and/or a type II variation.

II QUALITY ASPECTS

II.1 Introduction

This is a national application made under Article 8.3(i) for marketing authorisation of a combined conjugate vaccine, Menitorix composed of *Neisseria meningitidis* serogroup C (Men C) and *Haemophilus influenzae* type b capsular polysaccharides (Hib) (each 5 μg) conjugated to tetanus toxoid (5 μg and 12.5 μg for the respective Men C and PRP saccharides).

Other ingredients consist of the pharmaceutical excipients
Powder:
Trometamol (Tris)
Sucrose
Solvent:
Sodium chloride
Water for injection

The product is supplied as a pack of either 1 or 10 vials of Menitorix packaged together with an equal number of pre-filled syringes of solvent (0.5ml) with or without separate needles. Prior to administration, Menitorix must be reconstituted with the liquid saline diluent.

II.2 DRUG SUBSTANCE

The active ingredients of Menitorix are *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroup C conjugates, which are derived from the bacterial strains H. *influenzae* type b identified as Hib strain number S20752 and N. *meningitidis* serogroup C, strain C11 (recommended by the WHO for the manufacture of meningococcal vaccines).

Haemophilus type b polysaccharide consists of a repeating polymer of D-ribosyl and ribitol phosphate linked through a 1,1 linkage.

Manufacture occurs at a site where acceptable standards of GMP are in place.

The purified *Neisseria meningitidis* type C polysaccharide coded PSC, consists of partly O-acetylated repeating units of sialic acid, linked with 2α→9 glycosidic bonds (i.e. polymer of N-acetyl-O-acetylneuraminic acid).

Manufacture occurs at a site where acceptable standards of GMP are in place at this site.

The purified concentrated tetanus toxoid is manufactured at a site with acceptable standards of GMP are in place.

II.3 DRUG PRODUCT

Pharmaceutical development

Menitorix is a combined Hib-MenC conjugate vaccine composed of the purified capsular polysaccharides of *Haemophilus influenzae* type b and *Neisseria meningitidis* type C, each conjugated to tetanus toxoid. These are coded, respectively: PRP-TT and PSC-TT. Conjugation of PSC to the purified tetanus toxoid is novel to this product.

Menitorix vaccine is a lyophilised preparation, presented in monodose glass vials to be reconstituted with a liquid diluent just before injection. Vaccine vials and diluent syringes are packed together in a monodose package.

The manufacture and control of the final product are considered suitable for the indications proposed. The overall quality of the final product is satisfactory for its intended purpose.

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory.

The ingredients listed other than the active substances are: Tris, sucrose, sodium chloride and water which are all compliant with Ph. Eur requirements.

The list of culture ingredients used to produce Hib and Men C components has been assessed and there are no outstanding TSE issues.

None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used.

Glass containers meet Ph. Eur. standards. The closure is a type butyl D/12mm which meets Ph Eur requirements for rubber closures.

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale and has shown satisfactory results.

Finished Product Specification
The finished product specification is satisfactory. Test methods have been described and adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished products stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years with a storage conditions 'Store in a refrigerator (2ºC – 8ºC).', 'Do not freeze' and 'Store in the original package in order to protect from light' is set. This is satisfactory.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS
III.1 Introduction
This is a national application made under Article 8.3(i) for marketing authorisation of a combined conjugate vaccine, Menitorix composed of *Neisseria meningitidis* serogroup C (Men C) and *Haemophilus influenzae* type b capsular polysaccharides (Hib) (each 5 µg) conjugated to tetanus toxoid (5 µg and 12.5 µg for the respective Men C and PRP saccharides).

No specific non-clinical studies were performed with the Hib-MenC vaccine. Instead, the

applicant has assumed that the nonclinical studies (GLP compliant) performed with the Hib-MenCY vaccine will provide sufficient evidence for the absence of toxicity. The sole difference between the 2 products is the absence of the PSY-TT conjugate in the Hib-MenCY vaccine formulation. This is considered to be acceptable and the vaccine fulfils the conditions described in the CPMP Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines (CPMP/SWP/465/95).

III.2 Pharmacology

The immune response induced by Hib-MenCY vaccines was investigated in the context of a repeated-dose toxicity study in the rabbit where animals were treated five times with a 2-week interval between injections. Serological analysis showed the presence of circulating antibody titres against the MenC polysaccharide confirming an immunological response.

The Hib-MenCY test vaccine was found to be safe when assessed on the cardiovascular and respiratory systems of anaesthetized rats and administered either intravenously or intramuscularly at a several fold of the human dose, on a bodyweight basis.

III.3 Pharmacokinetics

Not applicable to vaccines.

III.4 Toxicology

The toxicological profile of the Hib-MenCY-TT vaccine was studied in a single dose and local tolerance study in the rabbit. There were no distinct changes in clinical signs or bodyweight and, macroscopically, no treatment-related changes were observed locally at the injection sites during the observation period or at necropsy.

Repeat-dose toxicity in rabbits did not lead to any distinct treatment-related changes in clinical signs, ophthalmoscopy, body temperature, body weight, food intake, haematology, clinical chemistry, relative and absolute organ weights and histopathology of the organs and tissues, other than of the injected muscles.

III.5 Environmental Risk Assessment

An Environmental Risk Assessment was included in the dossier. The report concluded that, “overall, it can be concluded that the constituents of Menitorix vaccine are unlikely to represent a risk for the environment following its prescribed usage in patients.”

III.6 Discussion on non-clinical aspects

There are no objections to the approval of Menitorix from a non-clinical point of view.

IV CLINICAL ASPECTS

IV.1 Introduction

This is a national application made under Article 8.3(i) for marketing authorisation of a combined conjugate vaccine, Menitorix composed of *Neisseria meningitidis* serogroup C (Men C) and *Haemophilus influenzae* type b capsular polysaccharides (Hib) (each 5 μg) conjugated to tetanus toxoid (5 μg and 12.5 μg for the respective Men C and PRP saccharides).

All clinical studies were conducted in accordance with Good Clinical Practice (GCP).

IV.2 Clinical Pharmacology

IV.3 Pharmacodynamics

Not applicable. The overview of data concerning immunogenicity of the vaccine is described in section IV.4 below.

IV.4 Efficacy

Formal studies of efficacy have not been performed since these would not be feasible. The demonstration of likely efficacy rests on the immunogenicity data assessed against the postulated serological correlates of protection. The comparability threshold antibody level for vaccine non-inferiority was determined to be 0.35 µg/ml using a reference non-22F inhibition ELISA (WHO guideline 2003). The derived equivalent threshold using the GSK 22F-inhibition ELISA is 0.20 µg/ml.

Although this application concerns the use of Hib-MenC 5/5 µg vaccine, data are also provided from investigations with a Hib-MenC 10/10 µg vaccine and experimental vaccines that contained various quantities of Hib, MenC and the meningococcal polysaccharide Y conjugated to tetanus toxoid (TT).

Summary tables of studies that provided primary series and booster/challenge data are provided on the next two pages. The applicant's claims for the schedules used are not correct. Very few of these studies actually used a schedule that reflected 2, 3 and 4 months. See descriptions of individual studies on this.

Because of the complex and evolving nature of the development programme that led up to this application, various formulations of the Hib-MenC 5/5 saccharide content vaccine have been assessed. Clinical data generated with the final chosen formulation (Third series lots) for the market came from the primary series study Hib-MenC-TT-012 and the booster study Hib-MenC-TT-011.

a. Number enrolled and dosed in primary vaccination studies

Vaccine	Study Abbreviation (Type) *(vaccine schedule)*	Number of administered doses	Number of subjects		
			Enrolled	Total vaccinated cohort	ATP immunogenicity cohort
Hib-MenC vaccine					
	MenC-TT-001 (Core and supportive) *(2-3-4 months)*	312	104	104	95
	Hib-MenC-TT-001 (Core) *(2-3-4 months)*	615	208	208	177
	Hib-MenCY-TT-003 (Core and supportive) *(2-3-4 months)*	233	78	78	74
Final formulation study	Hib-MenC-TT-012 (Core) *(2-3-4 months)*	1120	375	375	357
Subtotal of studies with the 2-3-4 month schedule		2280	765	765	703
	DTPa-HBV-IPV-097 (Core) *(2-4-6 months)*	351	125	117	111
Total		2631	890	882	814
Supportive formulations					
Hib-MenC 10/10	MenC-TT-001 (Core and supportive) *(2-3-4 months)*	302	101	101	94
Hib-MenCY 2.5/5/5 5/5/5 5/10/10	Hib-MenCY-TT-003 (Core and supportive) *(2-3-4 months)*	686	233	233	208
Subtotal of studies with the 2-3-4 month schedule		988	334	334	302
Hib-MenCY 2.5/5/5 5/5/5 5/10/10	Hib-MenCY-TT-001 (Supportive) *(2-4-6 months)*	725	245	244	225
Total		1713	579	578	527

b. Number enrolled and dosed in challenge/boostervaccination studies

Previous priming	Study Abbreviation (Extension of previous study)	Administration of Hib-MenC	Number of subjects			
			Enrolled	Total vaccinated cohort	ATP cohort of persistence	ATP immunogenicity cohort
Hib-MenC vaccine						
Hib-MenC	MenC-TT-008† (MenC-TT-001)	Challenge	94	94	90	83
Hib-MenC	Hib-MenCY-TT-004* (Hib-MenCY-TT-003)	Booster	44	44	44	42
Hib-MenC	Hib-MenC-TT-010 (DTPa-HBV-IPV-097)	Booster	87	87	84	81
NeisVac-C + DTPa containing vaccines	Hib-MenC-TT-010 (DTPa-HBV-IPV-097)	Booster	181	178	178	167
$MenC_{CRM197}$ conjugate vaccine + DTPa-Hib containing vaccines	Hib-MenC-TT-011 Final formulation Study	Booster	104	104	102	96
		Booster + MMR	102	102	101	96
Total with a challenge			94	94	90	83
Total with a booster			518	515	509	482
Supportive formulations						
Hib-MenC 10/10	MenC-TT-008† (MenC-TT-001)	Challenge	89	89	88	80
Hib-MenCY 2.5/5/5 5/5/5 5/10/10	Hib-MenCY-TT-002† (Hib-MenCY-TT-001)	Challenge	236	236	235	220
Hib-MenCY 2.5/5/5 5/5/5 5/10/10	Hib-MenCY-TT-004* (Hib-MenCY-TT-003)	Booster	134	133	133	123
Total with a challenge			325	325	323	300
Total with a booster			134	133	133	123

* In study Hib-MenCY-TT-004, the subjects received a booster dose of the same vaccines that they received in primary vaccination study Hib-MenCY-TT-003.

† In study MenC-TT-008, a dose of 10 μg of unconjugated PSC was administered (concomitantly with Infanrix™ hexa); in study Hib-MenCY-TT-002, a dose of 10 μg of unconjugated PSC and 10 μg of unconjugated PRP were administered concomitantly (challenge for immune memory).

The immunogenicity data resulted in the following conclusions:

Anti-MenC responses

- After primary series with three doses of Menitorix, Meningitec or Menjugate or two doses of NeisVac-C in infancy, SBA titres were highly satisfactory.
- SBA GMTs with Menitorix were numerically or significantly lower than those achieved by licensed comparators except in study DTaP-HBV-IPV-097 (at 2, 4, 6 months), in which the final GMT was highest in the Menitorix group.
- However, higher responses to Meningitec and Menjugate after the primary series did not translate into notably higher percentages still at 1:8 or 1:128 or higher GMTs pre-challenge or pre-boost compared to Hib-MenC 5/5-containing vaccines. Therefore, the differences in post-primary GMTs seem unlikely to be of clinical significance.

- Post-challenge with plain MenC saccharide the SBA GMTs were significantly higher in the Hib-MenC 5/5-containing vaccine groups compared to the Meningitec and Menjugate vaccine groups, suggesting an inverse relationship between the total conjugated saccharide administered in infancy and the response to a further dose of unconjugated MenC saccharide.
- With no staggered administration control group or DTwP control group, it is not possible to assess whether DTaP-containing vaccines depress the SBA GMTs achieved with Menitorix. Such a phenomenon has now been described in several studies with the licensed MenCC vaccines. The potential for this to occur has been mentioned in the Menitorix SmPC.
- Questions have been raised regarding the immunogenicity of Third series lots and the use of MenC-T to boost children primed with MenC-CRM197 conjugates. These can only be addressed by longer-term follow-up of immunogenicity and effectiveness.

Anti-PRP responses

- After a 3-dose primary series, the Hib-MenC 5/5 vaccine elicited ≥1 μg/ml anti-PRP in at least 97% of infants, with at least 93% reaching this level after the Hib-MenCY vaccine. GMCs were significantly higher after Menitorix than seen in the comparator groups that received Infanrix hexa.
- The lowest anti-PRP GMCs were seen in the studies that most closely adhered to a 2, 3 and 4-month schedule.
- Before the challenge/booster doses, almost all infants in the Menitorix groups still had ≥ 0.15 μg/ml anti-PRP and there was still an advantage in percentages with ≥ 1 μg/ml and in GMCs compared to the Infanrix hexa groups.
- Post-challenge suggested an inverse relationship between the amount of conjugated PRP administered in infancy and the later response to conjugated or unconjugated saccharide.
- Post-boost data with Menitorix, including with Third series lots, were highly satisfactory.
- The data support observations from other applications (e.g. that for Pediacel) that the response to PRP-T is better when MenC-T is co-administered or combined with it compared to co-administration of PRP-T with MenC-CRM197. Nevertheless, it must be questioned if these observations have any long-term relevance, especially for an invasive infection that is anyway rarely seen after the age of 4 years.

Two or three doses

There are two studies in the current dossier in which anti-MenC and anti-PRP data are available after the second and after the third doses. In MenC-TT-001, the data were from sampling at one month after dosing at approximately 3 and 4 months whereas the data from DTaP-HBV-IPV-097 pertain to sampling at two months after dosing at 2 and 4 months. Both datasets raise the possibility of administration of Menitorix in a 2-dose primary series.

Currently there is an ongoing study (014) in which two doses of Menitorix are being administered at 3 and 5 months of age. Data from this study and also from its planned booster phase may be able to confirm the suitability of a 2-dose regimen.

Responses to concomitant antigens

- Responses to diphtheria and tetanus toxoids were highly satisfactory and showed the expected effects of the conjugate protein administered on GMCs.
- Responses to HBsAg, IPV and, as far as can be judged based purely on comparability, pertussis antigens were similar between Hib-MenC 5/5 groups and the various control

groups.

- The data on co-administration with Prevenar are confined to study Hib-MenCY-TT-001. The important comparison between the ActHIB + Infanrix penta and Hib-MenCY 5/5/5 + Infanrix penta groups is confined to about 60-70 infants per group but it does show very similar responses to all seven serotypes.
- The data have been reflected in the Menitorix SmPC.

IV.5 Clinical Safety

In addition to the numbers shown in the table above there was another primary series study that provided only safety data (Hib-MenC-TT-003). This study set out to compare rates of fever > 39°C (rectal route) between Menitorix plus Infanrix penta (N-289) and Meningitec plus Infanrix hexa.
Thus, in primary series studies:

- 1171 infants were vaccinated with 3483 doses of 5/5 Hib-MenC
- 578 infants were vaccinated with 1713 doses of related formulations (Hib-MenC 10/10, Hib-MenCY 2.5/5/5, Hib-MenCY 5/5/5 or Hib-MenCY 5/10/10)

A 5/5 Hib-MenC booster dose was administered to 515 toddlers primed in infancy with 5/5 Hib-MenC (Hib-MenCY-TT-004 and Hib-MenC-TT-010), Hib combined with DTaP-containing vaccines (Hib-MenC-TT-010 and Hib-MenC-TT-011) or MenC-CRM_{197} conjugate (Hib-MenC-TT-011).
In these three booster studies, Hib-MenC was given alone (369) or was co-administered with Priorix (102) or Infanrix penta (44).

In all primary vaccination studies, there was a tendency for higher reporting of local symptoms at the Infanrix penta, Infanrix hexa and Pediacel injection sites than at the Hib-MenC or MenCC injection sites. The incidences of the three solicited local symptoms did not increase with subsequent doses except in study 012 in which there was a trend to increasing rates of local redness with consecutive doses of Menitorix although rates were lower than seen with the control group vaccines.

Redness was the most frequent local solicited symptom in all groups. Although redness was reported following 24.5% of Hib-MenC doses and in 39% of recipients, only 0.1% of Hib-MenC doses were followed by redness > 30 mm. Swelling was reported for 21.4% of infants after Hib-MenC compared to 39.3% after Menjugate and 0.4% of Hib-MenC doses were followed by swelling > 30mm compared to 0.2% - 0.6% for the three licensed MenCC vaccines.

In booster studies redness was the most frequently reported solicited local symptom at 5/5 Hib-MenC sites (31.4%) and the Menjugate site (29.5%). Large injection site reactions were reported in four children in study Hib-MenC-TT-010 of which two were boosted with Hib-MenC but there was no functional impairment and the events resolved.

General reactions **a**nd rates of unsolicited Adverse Events (AEs) after primary series and booster doses were similar or lower with Menitorix than seen in comparator group.

The single death seen in the clinical programme was not considered to be related to the study vaccines administered. The small number of Serious Adverse Events (SAEs) that have occurred with Hib-MenC 5/5 formulations do not seem likely to have been caused by the vaccine.

Overall the immunogenicity and safety data were considered to be satisfactory. However, it is clear that long-term follow-up of immunogenicity and effectiveness will be very important. In this light, the following studies are ongoing:

- **Hib-MenC-TT-013** is the ongoing extension of study 012, described in III.2.
- **Hib-MenC-TT-014** is an ongoing study in Italy and Finland in which two doses of Menitorix are administered at 3 and 5 months with Infanrix penta and compared to NeisVac-C plus Infanrix hexa.
- **Hib-MenC-TT-15** is the booster dose extension of 014 as above.
- **Hib-MenC-TT-016** is an ongoing study in which Menitorix is being used to boost Australian toddlers already primed with the nationally recommended vaccines and schedule.
- **Hib-MenC-TT-022** is the long-term follow-up of antibody persistence in children enrolled into studies 097 and 010.
- **Hib-MenC-TT-017-021** will follow-up children enrolled into 016 as above.

- Menitorix is also being used in one arm of a primary series study with the applicant's candidate pneumococcal vaccine (10 Pn-PD-DiT-011).

IV.6 Risk Management Plan

The marketing authorisation holder has submitted an RMP to the UK MHRA at the time of initial licensure, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Menitorix.

IV.7 Discussion of the clinical aspects

There are no objections to the approval of these applications from a clinical point of view.

V USER CONSULTATION

A user consultation with target patient groups on the PIL has been performed.

VI. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

There are no major quality objections to this application and all minor points have been clarified.

The process of manufacture was subject to a number of changes to the production of the Hib and MenC components that were well documented by the applicant. A quality comparison of these components after these changes had been introduced did not establish any differences caused by these changes. However, although the applicant used state of the art techniques, which were performed in addition to the applicant's obligation to show conformity with the Ph Eur requirements, it is notoriously difficult to completely characterise these complex products using the current state of the art analysis.

NON-CLINICAL

There are no non-clinical reasons why a marketing authorisation should not be granted.

There are no non-clinical points for clarification.

EFFICACY

Formal studies of efficacy have not been performed since these would not be feasible. The

demonstration of likely efficacy rests on the immunogenicity data assessed against the postulated serological correlates of protection.

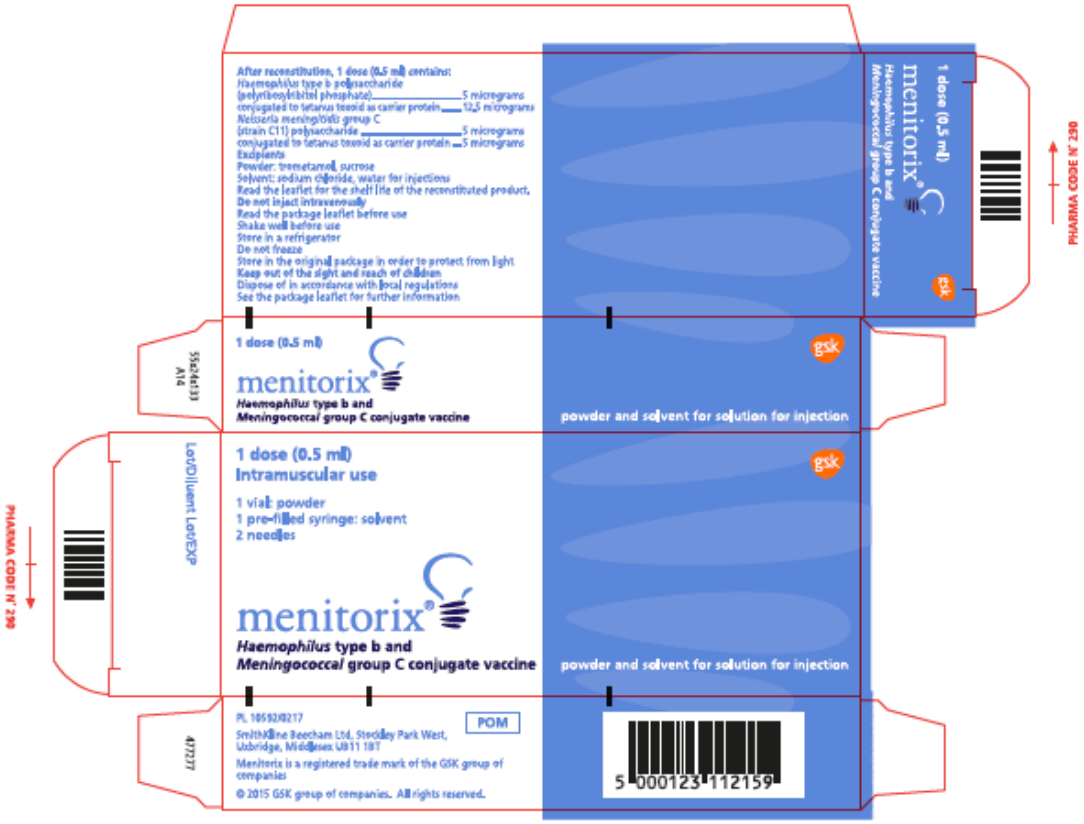
SAFETY

The data do not raise any unexpected or serious issues over the likely safety of Menitorix in clinical use.

PRODUCT LITERATURE

The approved SmPCs and PILs are satisfactory and in-line with those for products of this type. The final labelling is satisfactory and in-line with current guidelines.

The current approved UK SmPCs and PIL are available on the MHRA website. The current approved UK labelling is provided below.



RISK-BENEFIT ASSESSMENT

The UK considers that the risk benefit relationship for the use of Menitorix as detailed in the SmPC is favourable.

The new data that have become available since the initial grant of the UK licence and which have been added to mutual recognition application dossier do not change that opinion.

Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

(Type II variations, PSURs, commitments)

Scope	**Procedure number**	**Product information affected**	**Date of start of the procedure**	**Date of end of procedure**	**Approval/ non approval**	**Assessment report attached Y/N (version)**
II	UK/H/0954/001/II/018	SmPC (sections 4.2 and 5.1)	20/7/2010	8/12/2010	Approval	No
II	UK/W/0028/pdWS/005	N/A: study submission.	10/05/2013	30/09/2013	Approval	Yes
II	UK/H/0954/001/II/071	SmPC/PIL	14/08/2015	29/02/2016	Approval	Yes

Annex I

Reference:	PL 10592/0217 - 0069 - (UK/W/0028/pdWS/005);
Product:	Menitorix
Marketing Authorisation Holder:	GlaxoSmithKline Biologicals s.a.
Active Ingredients:	*Haemophilus influenzae* type b conjugate, *Neisseria meningitidis* capsular polysaccharide C, tetanus toxoid conjugates

Reason:	To submit an annex report on a study for Menitorix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. The specific study concerned. A phase III, open, randomized, controlled, multi-centre study to demonstrate the non-inferiority of the meningococcal serogroup C and the *Haemophilus influenzae* type b immune response of GlaxoSmithKline (GSK) Biologicals' conjugate Hib-MenC vaccine co-administered with GSK Biologicals' measles-mumps-rubella vaccine, Priorix™, versus MenC-CRM197 conjugate vaccine coadministered with GSK Biologicals' Hib vaccine, Hiberix™, and Priorix™ in 12- to 18-month-old toddlers primed in infancy with a Hib vaccine but not with a meningococcal serogroup C vaccine; and to evaluate the long-term antibody persistence up to 5 years after the administration of the Hib-MenC vaccine.

I. EXECUTIVE SUMMARY

Summary of outcome

The Marketing Authoriastion Holder (MAH) has submitted an annex report on a study for Menitorix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. The submission is, in general, satisfactory in terms of addressing the requirements of the MAH under Article 46 of Regulation (EC) No1901/2006, as amended.
The Rapporteur concludes that the benefit/risk for Menitorix is unchanged by data submitted in the current report and that there is no consequential need for regulatory action.

II. RECOMMENDATION

The benefit/risk for Menitorix is unchanged by data submitted in the current report and there is no consequential need for regulatory action. A variation to update the summary of product characteristics was submitted to align the results of the study has been submitted and approved, under PL 10592/0217 – 0069.

III. INTRODUCTION

On 13th June 2013, the MAH submitted an annex report on a study for Menitorix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

Menitorix is a conjugate Hib-MenC vaccine. This report presents the analysis of antibody persistence at 5 years after vaccination when co-administered with Priorix (measles-mumps-rubella vaccine) to 12- to 18-month old toddlers. The study is a non-inferiority study versus MenC-CRM197 conjugate vaccine co-administered with GSK Biologicals' Hib vaccine, Hiberix™ (*Haemophilus influenzae* type b tetanus toxoid conjugate vaccine), and Priorix™.

The MAH states that the data submitted thus far do not influence the benefit / risk for Menitorix and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study

Menitorix was first approved in the UK in December 2005 and registered in IE, BE, EL, ES and PL via UK/H/954/01/MR in 2008.

IV.2 Clinical aspects

IV.2.1 Introduction

The MAH has previously submitted data via article 46 procedures UK/W/028/pdWS/001, 002 and 004.

The MAH now submits annex report 5 to the 106445 (Hib-MenC-TT-016) study report:

- Hib-MenC-TT-021 (EXT: 016 Y5);

The MAH states that further regulatory action is not needed. The grounds for this claim are as follows: "*The current SmPC for Menitorix does not include Menitorix vaccination in Hib primed, but MenC naive toddlers (Hib-MenC-TT-016). Study Hib-MenC-TT-021 is the year 5 antibody persistence study of study Hib-MenC-TT-016. Study Hib-MenC-TT-016 and the year 1, 2, 3 and 4 year persistence follow-up studies Hib-MenC-TT-017, -018, -019 and -020 were reviewed in a previous Art 46 Work Sharing procedure (UK/W/028/pdWS/001, 002 and 004).In this review the assessor agreed that the data from study Hib-MenC-TT-016 and the related persistence studies do not require any regulatory action".*

Clinical study

Assessor comment: the study has been described in previous annual assessments: this report summarises the main points only.

Study title

A phase III, open, randomized, controlled, multi-centre study to demonstrate the non-inferiority of the meningococcal serogroup C and the *Haemophilus influenzae* type b immune response of GlaxoSmithKline (GSK) Biologicals' conjugate Hib-MenC vaccine co-administered with GSK Biologicals' measles-mumps-rubella vaccine, Priorix™, versus MenC-CRM197 conjugate vaccine coadministered with GSK Biologicals' Hib vaccine, Hiberix™, and Priorix™ in 12- to 18-month-old toddlers primed in infancy with a Hib vaccine but not with a meningococcal serogroup C vaccine; and to evaluate the long-term antibody persistence up to 5 years after the administration of the Hib-MenC vaccine.

This study has two phases: the vaccination phase 106445 (Hib-MenC-TT-016) and the long-term persistence phase (Hib-MenC-TT-017 EXT: 016 Y1 to Hib-MenC-TT-021 EXT: 016 Y5) with assessments of persistence at 1, 2, 3, 4 and 5 years after vaccination.

This study has been conducted by seven principal investigators in Australia.

Objectives

The co-primary objectives, which were both related to the vaccination phase of the study, were to demonstrate non-inferiority of Menitorix vs. MenC-CRM197 and Hiberix at one month post-vaccination in terms of:

- Percentage of subjects with rSBA-MenC titre ≥1:8
- Percentage of subjects with anti-PRP concentration ≥0.15 µg/ml

The criteria for non-inferiority were based on the lower limits of the standardised asymptotic 95% confidence intervals on the differences being above -10%.

The secondary objective, that was related to the persistence data at 1, 2, 3, 4 and 5 years after vaccination, was to evaluate the long-term persistence of the immune response induced by Hib-MenC compared to separately administered Hiberix™ and MenC-CRM_{197}, when both groups received a separate concomitant injection of Priorix™.

Study design

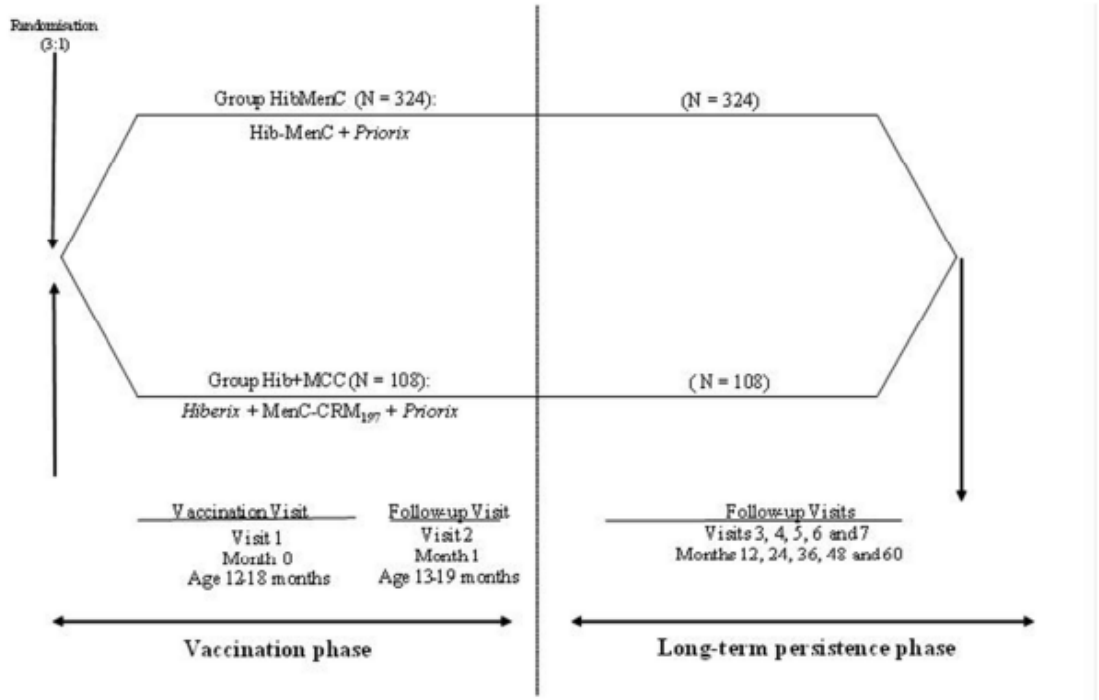
Open, randomized (3:1), controlled, multi-centre study with two parallel groups.

Vaccine was not administered during the long term persistence phase of the study

A blood sample was collected from subjects in both groups at pre-specified time-points after vaccination, as described.

The study design is summarised in the following diagram:

5.1.1. Overall study design – Description



Note: The actual number of subjects enrolled in the Year 5 long-term persistence phase of the study was 217 in the HibMenC group and 78 in the Hib+MCC group.

Study procedures during the long-term persistence phase are summarised in the following table:

Table 1 List of study procedures during the long-term persistence phase of the study

Age Visit Timing Post vacc I Year x	2-2.5 y VISIT 3 Month 12 Post vacc I	3-3.5 y VISIT 4 Month 24 Post vacc I	4-4.5 y VISIT 5 Month 36 Post vacc I	5-5.5 y VISIT 6 Month 48 Post vacc I	6-6.5 y VISIT 7 Month 60 Post vacc I
Check exclusion criteria for the long-term persistence	●	●	●	●	●
Meningococcal medical history since last visit	●	●	●	●	●
Meningococcal vaccination history since last visit	●	●	●	●	●
Hib medical history since last visit	●	●	●	●	●
Hib vaccination history since last visit	●	●	●	●	●
Physical examination	●	●	●	●	●
Blood sampling: for antibody determination (3.5 mL)	●	●	●	●	●
Tracking document	●	●	●	●	●
Retrospective recording of Serious Adverse Events* since last visit	●	●	●	●	●
Retrospective recording of relevant medication since last visit**	●	●	●	●	●
Conclusion	●	●	●	●	●

● was used to indicate a study procedure that required documentation in the individual eCRF.
* At each visit of the long-term persistence phase (i.e. at 1 year up to 5 years after vaccination), the subject's parents/guardians were to be asked retrospectively if any SAE had occurred since the last visit of the previous year. Only those SAEs that were determined by the investigator to have a causal relationship to the vaccination were to be described individually in the study report, along with the nature of the SAEs and the outcome. Any event related to lack of vaccine efficacy during the long-term persistence phase or related to study participation were to be described in details.
**Relevant medication included any immunosuppressant(s) or other immune-modifying drug(s), immunoglobulins and/or any blood products.

Study population

The population studied is summarised in the following tables:

Table 16 Summary of demographic characteristics (ATP cohort for persistence Year 5)

		HibMenC N = 195		Hib+MCC N = 68		Total N = 263	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (Month) at vaccination	N	195	-	68	-	263	-
	Mean	12.58	-	12.44	-	12.55	-
	SD	1.00	-	0.76	-	0.95	-
	Median	12.00	-	12.00	-	12.00	-
	Minimum	12.00	-	12.00	-	12.00	-
	Maximum	17.00	-	15.00	-	17.00	-
Age (Month) at Year 5	N	195	-	68	-	263	-
	Mean	72.41	-	72.26	-	72.37	-
	SD	1.09	-	0.96	-	1.05	-
	Median	72.00	-	72.00	-	72.00	-
	Minimum	71.00	-	71.00	-	71.00	-
	Maximum	77.00	-	75.00	-	77.00	-
Vaccination History	DTPa/Hib	137	70.3	50	73.5	187	71.1
	Hib-OMP	58	29.7	18	26.5	76	28.9
Gender	Female	88	45.1	24	35.3	112	42.6
	Male	107	54.9	44	64.7	151	57.4
Race	African heritage / African American	0	0	0	0	0	0
	American Indian or Alaskan Native	0	0	0	0	0	0
	Asian - Central/South Asian heritage	3	1.5	0	0	3	1.1
	Asian - East Asian heritage	4	2.1	1	1.5	5	1.9
	Asian - Japanese heritage	1	0.5	0	0	1	0.4
	Asian - South East Asian heritage	2	1.0	0	0	2	0.8
	Native Hawaiian or Other Pacific Islander	1	0.5	0	0	1	0.4
	White - Arabic / North African heritage	4	2.1	0	0	4	1.5
	White - Caucasian / European heritage	168	86.2	65	95.6	233	88.6
	Other*	12	6.2	2	2.9	14	5.3

HibMenC = Vaccinated with Hib-MenC + *Priorix*
Hib+MCC = Vaccinated with *Hiberix* + *Meningitec* + *Priorix*
DTPa/Hib = Primed through three doses of DTPa/Hib
Hib-OMP = Primed through two doses of Hib-OMP
N = total number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = Standard deviation
Other* (race) = Anglo-Indian (2), Arabic/Caucasian (1), East Asian/White (1), Caucasian Anglo/Ind (1), Caucasian Indonesian (1), Caucasian/Kurdish (1), Chinese/Indian/Maori (1), Dad Arabic Mum Cauca (1), Eurasian (1), Indian/Japanese/Caucasian (1), Indian/American (1), Indigenous Australian (1), Pacific Islander-Fij(1)

The tracking log-sheets for all subjects initially vaccinated in the primary study 106445 (HIb-MenC-TT-016) until the year 5 time points are presented in the following table:

Of the 433 subjects who were enrolled and vaccinated in study 106445 (Hib-MenC-TT-016), 138 did not participate in this study: 6 subjects were not eligible, 28 were lost to follow-up and 104 subjects did not participate because of another reason other than the occurrence of an AE or SAE. No subject declined participation due to an AE or SAE

10.1.1. Number of subjects

Table 6 Summary of tracking log-sheets for all subjects initially vaccinated in the primary study 106445 (Primary Total Vaccinated cohort)

	HibMenC N = 324		Hib+MCC N = 109		Total N = 433	
	n	%	n	%	n	%
Not participating to 106454	107	33.0	31	28.4	138	31.9
Not eligible	3	0.9	3	2.8	6	1.4
Lost to follow-up	21	6.5	7	6.4	28	6.5
Not willing to participate due to AE or SAE	0	0.0	0	0.0	0	0.0
Not willing to participate due to other reason	83	25.6	21	19.3	104	24.0
Died	0	0.0	0	0.0	0	0.0
Enrolled in 106454	217	67.0	78	71.6	295	68.1

HibMenC = Vaccinated with Hib-MenC + *Priorix*
Hib+MCC = Vaccinated with *Hiberix* + *Meningitec* + *Priorix*
N = number of subjects vaccinated in the initial study
n/% = number/percentage of subjects in a given category

Protocol deviations

Of the 295 subjects included in the Total Enrolled Cohort Year 5, 32 subjects were eliminated from the ATP cohort for persistence Year 5 for reasons specified in the following table:

Table 10 Number of subjects enrolled into the study as well as number excluded from ATP persistence analyses with reason for exclusion

	Total			HibMenC		Hib+MCC	
Title	n	s	%	n	s	n	s
Total vaccinated cohort in 106445 study	433			324		109	
Subjects who did not come for Year 5 visit (code 900)	138	138		107	107	31	31
Total Enrolled Cohort Year 5	295		100	217		78	
Administration of vaccine(s) forbidden in the protocol (code 1040)	6	6		3	3	3	3
Others (code 1500)	12	12		10	10	2	2
Administration of any medication forbidden by the protocol (code 2040)	1	1		1	1	0	0
Essential serological data missing (code 2100)	13	13		8	8	5	5
ATP cohort for persistence Year 5	263		89.2	195		68	

HibMenC = Vaccinated with Hib-MenC + *Priorix*
Hib+MCC = Vaccinated with *Hiberix* + *Meningitec* + *Priorix*
Note - Subjects may have more than one elimination code assigned
n - number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s - number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total Enrolled Cohort Year 5

The 12 subjects who were eliminated for other reasons (elimination code 1500) included protocol violations linked to the eligibility criteria but not age (mainly completion of primary vaccination with 2 doses of Hib-OMP or 3 doses of DTPa/Hib-TT containing vaccine at least 6 months before start of the vaccination phase).

Amendment 3

Protocol Amendment 3 is dated 27th March 2012. Amendment 3 is as follows:

To support the data obtained by serum bactericidal assay testing, antibody concentrations against meningococcal polysaccharide (anti-PSC) were planned to be assessed by enzyme-linked immunosorbent assay (ELISA). The ELISA testing was stopped at 3 years after vaccine administration for the following reasons:

- the World Health Organisation (WHO) considers serum bactericidal assay testing the primary means of assessing immune response to meningococcal conjugate vaccines [WHO, 2006; WHO, 1999]

- circulating bactericidal antibodies are more critical for persistent protection against meningococcal disease than non-functional antibodies against meningococcal polysaccharides [CDC, 2011;WHO, 2006].

The rabbit serum bactericidal assay testing was done at GSK Biologicals' laboratory for the blood samples taken before vaccination and 1, 2 and 3 years after vaccination, while the rabbit serum bactericidal assay testing at 4 and years after vaccination was done at the laboratory of the Health Protection Agency in the United Kingdom.
The anti-PRP (polyribosylribitol phosphate) testing was done at GSK Biologicals' laboratory for all time-points.

Assessor comment: it is confirmed that the WHO and CDC advise on serum bactericidal assay testing as the more informative assay

Results

For the Year 5 persistence time point, the first volunteer was enrolled in the study on 17 June 2011 and the last study visit was on 03 October 2012. The first visit in the primary study 106445 (Hib-MenC-TT-016) took place on 19 June 2006.

The primary analysis of immunogenicity was based on the ATP cohort for persistence Year 5.

The rabbit serum bactericidal assay MenC testing was performed at the Health Protection Agency, UK at Years 4 and 5 compared to previous years at GSK laboratories and so the rabbit serum bactericidal assay -MenC antibody titre results at Years 4 and 5 cannot be directly compared with previous years. Results for years 4 and 5 are shown in the following table:

Percentage of subjects with HPA rSBA-MenC titres equal to or above 1:8 or 1:128 and GMTs (ATP cohort for persistence Year 5)

				≥ 1:8				≥ 1:128				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
rSBA-MenC	HibMenC	PI(M48)	183	22	12.0	7.7	17.6	5	2.7	0.9	6.3	5.3	4.7	5.9
		PI(M60)	195	37	19.0	13.7	25.2	12	6.2	3.2	10.5	6.6	5.6	7.8
	Hib+MCC	PI(M48)	64	9	14.1	6.6	25.0	4	6.3	1.7	15.2	6.4	4.6	8.8
		PI(M60)	68	17	25.0	15.3	37.0	7	10.3	4.2	20.1	8.5	5.9	12.3

HibMenC = Vaccinated with Hib-MenC + *Priorix*
Hib+MCC = Vaccinated with *Hiberix* + *Meningitec* + *Priorix*
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PI(M48) = Post-vaccination blood sample at Month 48
PI(M60) = Post-vaccination blood sample at Month 60

The co-primary objectives of the vaccination phase of the study were to demonstrate non-inferiority in terms of percentages of subjects with rSBA-MenC titres ≥1:8 and percentages of subjects with anti-PRP antibody concentrations ≥0.15g/ml at one month post-vaccination.

At 5 years following vaccination, the percentage of subjects with rSBA-MenC titre ≥1:8 was 19% of the subjects in the HibMenC group and 25% of the subjects in the Hib+MCC group.

Assessor comment: the co-primary objectives of the vaccination phase of the study were met with regards to the rSBA-MenC titres

The data on PRP (polyribosylribitol phosphate) testing, for which laboratory and method remained the same throughout the different time-points of this persistence study, are as shown in the following table:

Percentage of subjects with anti-PRP concentrations greater than or equal to 0.15 micrograms per mL and 1.0 micrograms per mL and GMCs (ATP cohort for persistence Year 5)

				≥ 0.15 µg/mL				≥ 1 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	value	**LL**	**UL**
Anti-PRP	HibMenC	PRE	192	152	79.2	72.7	84.7	50	26.0	20.0	32.9	0.439	0.365	0.529
		PI(M1)	193	193	100	98.1	100	190	98.4	95.5	99.7	46.550	37.412	57.919
		PI(M12)	175	174	99.4	96.9	100	141	80.6	73.9	86.2	3.463	2.806	4.273
		PI(M24)	178	176	98.9	96.0	99.9	128	71.9	64.7	78.4	2.528	2.057	3.107
		PI(M36)	187	185	98.9	96.2	99.9	129	69.0	61.8	75.5	2.179	1.798	2.641
		PI(M48)	178	176	98.9	96.0	99.9	126	70.8	63.5	77.3	2.079	1.719	2.514
		PI(M60)	191	191	100	98.1	100	129	67.5	60.4	74.1	2.131	1.752	2.592
	Hib+MCC	PRE	67	52	77.6	65.8	86.9	13	19.4	10.8	30.9	0.407	0.292	0.568
		PI(M1)	67	67	100	94.6	100	67	100	94.6	100	66.848	49.413	90.434
		PI(M12)	64	64	100	94.4	100	55	85.9	75.0	93.4	4.577	3.298	6.352
		PI(M24)	61	61	100	94.1	100	51	83.6	71.9	91.8	3.274	2.402	4.463
		PI(M36)	63	62	98.4	91.5	100	50	79.4	67.3	88.5	2.668	1.952	3.646
		PI(M48)	64	64	100	94.4	100	50	78.1	66.0	87.5	3.070	2.220	4.246
		PI(M60)	67	67	100	94.6	100	47	70.1	57.7	80.7	2.537	1.815	3.546

HibMenC = Vaccinated with Hib-MenC + *Priorix*
Hib+MCC = Vaccinated with *Hiberix* + *Meningitec* + *Priorix*
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination
PI(M1) = Post-vaccination blood sample at Month 1
PI(M12) = Post-vaccination blood sample at Month 12
PI(M24) = Post-vaccination blood sample at Month 24
PI(M36) = Post-vaccination blood sample at Month 36
PI(M48) = Post-vaccination blood sample at Month 48
PI(M60) = Post-vaccination blood sample at Month 60

- At 5 years post-vaccination, anti-PRP concentrations ≥0.15 µg/mL was observed for all subjects in the HibMenC group and all subjects of the Hib+MCC group.

Assessor comment: the co-primary objectives of the study were met with regards to the anti-PRP concentrations.

Since the percentage of subjects who came back for the Year 5 follow-up visit with serological results available excluded from the ATP cohort for persistence Year 5 was more than 5% in the HibMenC and the Hib+MCC group, a second analysis based on the Total Enrolled Cohort Year 5 was performed to complement the ATP analysis and these results were consistent with those for the ATP cohort for persistence Year 5.

Safety

No serious adverse events considered related to vaccination by the investigator were reported between the end of the vaccination phase and the Year 5 follow-up visit.

Conclusion submitted by Company:

At Year 5:

- Percentage of subjects with rSBA-MenC titre ≥1:8 was 19% of the subjects in the HibMenC group and 25% of the subjects in the Hib+MCC group.
- Anti-PRP concentrations ≥0.15 µg/mL was observed for all subjects in the HibMenC group and all subjects of the Hib+MCC group.
- No serious adverse events considered as related to vaccination by the investigator or events related to lack of vaccine efficacy were reported between the end of the vaccination phase of the study and the Year 5 follow-up visit.

IV.2.2 Discussion on clinical aspects
The co-primary objectives of the vaccination phase of the study were met.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Overall Conclusion
The submission is, in general, satisfactory in terms of addressing the requirements of the MAH under Article 46 of Regulation (EC) No1901/2006, as amended.

Recommendation
The Rapporteur concludes that the benefit / risk for Menitorix is unchanged by data submitted in the current report and that there is no consequential need for regulatory action.

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

MAH	Name of the medicinal product	Strength	Pharmaceutical form	AS
GlaxoSmithKline	Menitorix		Power and solvent for solution for injection	5µg *Haemophilus influenzae* type b capsular polysaccharide conjugated to 12.5µg tetanus toxoid; 5µg *Neisseria meningitidis* serogroup C capsular polysaccharide conjugated to 5µg tetanus toxoid

Annex II

Reference:	PL 10592/0217 - 0107 - (UK/H/0954/001/II/071);
Product:	Menitorix
Marketing Authorisation Holder:	GlaxoSmithKline Biologicals s.a.
Active Ingredients:	*Haemophilus influenzae* type b conjugate, *Neisseria meningitidis* capsular polysaccharide C, tetanus toxoid conjugates
Reason	To update sections 2, 4.4 and 5.1 of the SmPC with data from the M72 time-point from study Hib-MenC-TT 035 M72 in Q3 2014. Consequentially the label and leaflet have been updated.

Background

Menitorix is a Hib-MenC-TT conjugate vaccine. It is indicated for the prevention of invasive diseases caused by *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* serogroup C (MenC). Menitorix is indicated for primary vaccination in infants from 6 weeks of age up to 12 months of age (i.e., three doses should be given as of 6 weeks of age with at least one month between doses). A single may be used in the second year of life (from the age of 12 months onwards and before the age of 2 years) to boost immunity to Hib and MenC in toddlers who were primed in infancy with a Menitorix 3-dose series, or other Hib or MenC conjugate vaccines.

A single (0.5 ml) dose of Menitorix may also be used in toddlers to elicit immunity against MenC and to boost immunity to Hib in MenC unprimed toddlers. The timing of the booster dose should be in accordance with available official recommendations and should usually be from the age of 12 months onwards and before the age of 2 years.

The first approval of Menitorix was obtained in the United Kingdom (UK) on 19 December 2005. Currently Menitorix is licensed in seven countries (Australia, Belgium, Brazil, Ireland, New-Zealand, Poland, and the UK).

An Article 46 requires the marketing authorisation holder to submit information on studies conducted in children of authorised medicines that have been completed since the Paediatric Regulation came into force on 26 January 2007. A commitment was taken during an Article 46 procedure - UK/W/0028/pdWS/006. This type II variation was submitted in order to update section 5.1 of the SmPC with results from M72 time-point from study Hib-MenC-TT 035 M72 in Q3 2014. The MAH also took the opportunity to make minor corrections to the SmPC, labelling and package leaflet.

Supporting Evidence

The MAH submitted an annex report for study Hib-MenC-TT-035 EXT:10PN-PD-DiT-017, a phase III, open, multicentre study to assess the long-term antibody persistence in children up to 6 years of age who previously received full vaccination course (primary and booster vaccination) with Hib-MenC or MenC conjugate vaccines (MenC-CRM197 conjugate vaccine - Meningitec or MenC-TT conjugate vaccine - NeisVac-C) co-administered with DTPa-containing and pneumococcal conjugate vaccines (GSK Biologicals' 10Pn-PD-DiT or Prevenar) in the primary vaccination study 10PN-PDDiT-011 (107005) and booster vaccination study 10PN-PD-DiT-017 BST: 011 (109507).

Description

This is an open label study of post-booster antibody persistence that was initiated in May 2009 and conducted at multiple study sites in three countries (Germany, Poland, and Spain). Subjects have remained in the same four parallel groups as assigned in the primary (10PN-PDDiT-011) and booster (10PN-PD-DiT-017BST: 011) phases.
This annex report includes the antibody persistence results from 5 year's post-booster vaccination (i.e. in children of 6 years of age), except for those of anti-HBs persistence, which will be communicated in another annex report.

Objective(s)

Primary

- To evaluate the antibody persistence with respect to the MenC component of the Hib-MenC conjugate vaccine in terms of percentage of subjects with serum bactericidal assay using rabbit complement rSBA-MenC titres ≥ 1:8.

Secondary

- To evaluate the antibody persistence with respect to the components of the Hib-MenC conjugate vaccine in terms of rSBA-MenC titres and anti-polyribosylribitol phosphate (anti-PRP) antibody concentrations.
- To evaluate the antibody persistence with respect to the components of the pneumococcal conjugate vaccine in terms of antibody concentrations against vaccine pneumococcal serotypes.

Study design

This study was an open study and an extension of the primary vaccination study 10PN-PDDIT- 011 and the booster vaccination study 10PN-PD-DIT-017 BST: 011. During the persistence phases of this study, a total of three blood samples (approximately 5 mL per sample) were taken when the subjects were 3, 4 and 6 years of age (at approximately 2, 3 and 5 years post-booster vaccination, respectively).

Study population

- Healthy male or female subjects between, and including, 36 and 40 months of age at the first post-boost visit;
- Written informed consent obtained from the parent or guardian of the subject;
- Subjects who previously participated in the 10PN-PD-DiT-011 and the 10PN-PD-DiT-017 BST: 011 studies, who received a full vaccination course with the vaccines corresponding to their group during the primary and booster studies and who were part, in the 10PN-PD-DIT-017 BST: 011 study, of the blood sampling subset.

Treatments

- **Group 10Pn + Hib-MenC** (**Pn-HibC** in tables):
  - Menitorix + 10Pn-PD-DiT + Infanrix penta as primary vaccination
  - Menitorix + 10Pn-PD-DiT + Infanrix penta(1) -Infanrix IPV(2) as booster vaccination
- **Group Prevenar + Hib-MenC** (**Pr-HibC** in tables):
  - Menitorix + Prevenar + Infanrix penta as primary vaccination
  - Menitorix + Prevenar + Infanrix penta(1)-Infanrix IPV(2) as booster vaccination
- **Group 10Pn + MenC-CRM** (**Pn-Men** in tables):
  - Meningitec(3) + 10Pn-PD-DiT + Infanrix hexa as primary vaccination
  - Meningitec + 10Pn-PD-DiT + Infanrix hexa(1)-Infanrix IPV/Hib(2) as booster vaccination
- **Group 10Pn + MenC-TT** (**Pn-Neis** in tables):

- NeisVac-C(3) + 10Pn-PD-DiT + Infanrix hexa as primary vaccination
- NeisVac-C + 10Pn-PD-DiT + Infanrix hexa(1)-Infanrix IPV/Hib(2) as booster vaccination

(1) Germany and Poland
(2) applicable in Spain
(3) 2-dose primary vaccination in Germany and Spain, 3-dose primary vaccination in Poland
To comply with the national vaccination schedule, the Polish subjects of group Pn-Men and Pn-Neis received a third primary dose of Meningitec or NeisVac-C at the end of the primary vaccination phase (i.e. after the blood sample was taken at 7 months of age).

Outcomes/endpoints
- rSBA-MenC titres ≥ 1:8, ≥ 1:128 and geometric mean titres (GMTs)
- anti-PRP antibody concentrations ≥ 0.15 µg/ml, ≥ 1.0 µg/ml and concentrations
- antibody concentrations against vaccine pneumococcal serotypes

Statistical Methods
The primary analysis was based on the corresponding ATP cohort for persistence at 72 months of age. Since, for any vaccine group, the percent of enrolled subjects excluded from this ATP cohort was not more than 5%, a second analysis based on the Total enrolled cohort at 72 Months of age was not performed to complement the ATP analysis.

Where appropriate, for each treatment group, at each time-point that a blood-sample result was available and for each antigen tested at that time-point, in all subjects:

- antibody GMCs/GMTs with 95% confidence intervals (CIs) were tabulated;
- seropositivity/seroprotection rates and percentage of subjects with titres/concentrations above proposed cut-offs with exact 95% CIs were calculated.

Results
- Recruitment/ Number analysed

  The Total enrolled cohort at 72 months of age consisted of 539 subjects (out of 660 that were vaccinated in the booster study), of which 9 subjects (< 5%) were eliminated from the ATP cohort for persistence at 72 months of age.
- Baseline data

  The demographic profile of the Pn-Men, Pn-Neis, Pn-HibC and Pr-HibC groups of the ATP cohort for persistence at 72 months of age was similar with respect to mean age and racial distribution. Of note, a higher percentage of male subjects was included in group Pn-Neis (54% male subjects) and a higher percentage of female subjects was included in group Pn-HibC (59% female subjects).

		Pn-Men N = 128		Pn-Neis N = 137		Pn-HibC N = 131		Pr-HibC N = 134		Total N = 530	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age (months) at Visit 3	Mean	72.8	-	72.9	-	72.9	-	72.9	-	72.9	-
	SD	1.02	-	1.09	-	1.00	-	1.15	-	1.07	-
	Median	73.0	-	73.0	-	73.0	-	73.0	-	73.0	-
	Minimum	72	-	72	-	72	-	72	-	72	-
	Maximum	76	-	77	-	76	-	76	-	77	-
Gender	Female	63	49.2	63	46.0	77	58.8	68	50.7	271	51.1
	Male	65	50.8	74	54.0	54	41.2	66	49.3	259	48.9

Immunogenicity results

The rSBA-MenC test was performed at the Health Protection Agency (HPA) (now known as Public Health England [PHE]) lab at 72 months of age while the GSK lab was used for testing at 36 months and 48 months of age. Therefore, the rSBA-MenC antibody titre results at the 72 months of age timepoint cannot be directly compared with previous years. To reflect this difference, the rSBA-MenC tables are divided into two separate tables: one table presenting the post-primary vaccination, pre-booster vaccination, one month post-booster vaccination and 36 and 48 months of age timepoints tested at the GSK laboratory and the other table presenting the 72 months of age timepoint tested at the HPA laboratory.

Persistence of meningococcal antibodies

The percentage of subjects with HPA rSBA-MenC titre ≥ 1:8 at 72 months of age was 24.2% in Pn-Men group, 40.1% in Pn-Neis group, 38.5% in Pn-HibC group and 25.4% in Pr-HibC group. The percentage of subjects with HPA rSBA-MenC titre ≥ 1:128 was 8.6% in Pn-Men group, 13.9% in Pn-Neis group, 11.5% in Pn-HibC group and 10.4% in Pr- HibC group. GMTs ranged from 7.2 in the Pn-Men group to 11.9 in the Pn-Neis group.

rSBA-MenC

				≥ 1:8					≥ 1:128				GMT		
						95% CI					95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL		n	%	LL	UL	value	LL	UL
rSBA-MenC	Pn-Men	Post-Booster(72M of age)	128	31	24.2	17.1	32.6		11	8.6	4.4	14.9	7.2	5.8	8.9
	Pn-Neis	Post-Booster(72M of age)	137	55	40.1	31.9	48.9		19	13.9	8.6	20.8	11.9	8.9	16.0
	Pn-HibC	Post-Booster(72M of age)	130	50	38.5	30.1	47.4		15	11.5	6.6	18.3	10.1	7.9	12.9
	Pr-HibC	Post-Booster(72M of age)	134	34	25.4	18.3	33.6		14	10.4	5.8	16.9	8.5	6.6	11.1

Results obtained with Menitorix highlighted in yellow

The results of the previous tests performed by GSK are shown hereafter.

				≥ 1:8					≥ 1:128				GMT		
						95% CI					95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL		n	%	LL	UL	value	LL	UL
rSBA-MenC	Pn-Men	PII(M4)	124	122	98.4	94.3	99.8		119	96.0	90.8	98.7	1270.3	1019.9	1582.1
		PII(M5)	96	93	96.9	91.1	99.4		89	92.7	85.6	97.0	638.3	487.0	836.5
		Pre-Booster	52	45	86.5	74.2	94.4		21	40.4	27.0	54.9	73.8	48.6	112.2
		Post-Booster(M1)	74	74	100	95.1	100		73	98.6	92.7	100	2804.7	2141.6	3673.2
		Post-Booster(36M of age)	123	108	87.8	80.7	93.0		61	49.6	40.5	58.8	101.8	76.2	136.0
		Post-Booster(48M of age)	123	91	74.0	65.3	81.5		45	36.6	28.1	45.7	47.6	34.5	65.7
	Pn-Neis	PII(M4)	136	136	100	97.3	100		132	97.1	92.6	99.2	1470.1	1240.0	1742.9
		PII(M5)	103	103	100	96.5	100		100	97.1	91.7	99.4	1156.3	939.6	1423.0
		Pre-Booster	54	52	96.3	87.3	99.5		40	74.1	60.3	85.0	222.4	152.2	325.1
		Post-Booster(M1)	73	73	100	95.1	100		73	100	95.1	100	4638.1	3713.6	5792.8
		Post-Booster(36M of age)	134	133	99.3	95.9	100		103	76.9	68.8	83.7	250.3	201.5	311.0
		Post-Booster(48M of age)	129	124	96.1	91.2	98.7		76	58.9	49.9	67.5	150.6	118.5	191.3
	Pn-HibC	PII(M4)	128	124	96.9	92.2	99.1		114	89.1	82.3	93.9	487.7	383.5	620.2
		PIII(M5)	106	106	100	96.6	100		104	98.1	93.4	99.8	1589.4	1271.6	1986.7
		Pre-Booster	55	51	92.7	82.4	98.0		37	67.3	53.3	79.3	166.9	113.7	245.0
		Post-Booster(M1)	63	63	100	94.3	100		63	100	94.3	100	5112.0	3861.3	6767.7
		Post-Booster(36M of age)	126	111	88.1	81.1	93.2		84	66.7	57.7	74.8	158.0	115.4	216.4
		Post-Booster(48M of age)	120	99	82.5	74.5	88.8		68	56.7	47.3	65.7	103.6	73.9	145.3
	Pr-HibC	PII(M4)	125	122	97.6	93.1	99.5		111	88.8	81.9	93.7	479.2	381.7	601.5
		PIII(M5)	94	93	98.9	94.2	100		89	94.7	88.0	98.3	1232.0	947.6	1601.7
		Pre-Booster	66	58	87.9	77.5	94.6		42	63.6	50.9	75.1	137.2	94.3	199.8
		Post-Booster(M1)	62	62	100	94.2	100		60	96.8	88.8	99.6	3137.3	2288.8	4300.2
		Post-Booster(36M of age)	125	102	81.6	73.7	88.0		63	50.4	41.3	59.5	83.5	60.0	116.2
		Post-Booster(48M of age)	120	92	76.7	68.1	83.9		53	44.2	35.1	53.5	67.7	47.7	96.0

Five years post booster vaccination, the lowest percentage of seroprotected individuals was observed in the groups vaccinated with Meningitec (Pn-Men, 24.2% of subjects) and Menitorix with Prevenar (Pr-HibC, 25.4% of subjects) and the highest percentage in the group vaccinated with NeisVac-C (Pn-Neis, 40.1% of subjects). The same trend was observed when rSBA MenC titres above 1:128 were taken into account.

Persistence of *Haemophilus influenzae* type b antibodies

At 72 months of age, the percentage of subjects with anti-PRP concentrations ≥ 0.15 µg/mL was 99.2% in Pn-Men group, 98.5% in Pn-Neis group, 100% in Pn-HibC group and 100% in Pr-HibC group.

A higher percentage of subjects with anti-PRP antibody concentrations ≥ 1.0µg/ml was observed in subjects primed and boosted with Menitorix (84.6% in the Pn-HibC group and 75.8% in the Pr-HibC group) compared to subjects primed with Infanrix Hexa and boosted with a DTPa/Hib containing vaccine (66.9% in the Pn-Men group and 57.5% in the Pn-Neis group). Lower anti-PRP GMCs were observed in groups Pn-Men and Pn-Neis as compared to groups Pn-HibC and Pr-HibC.

Anti-PRP

				≥ 0.15 ug/ml				≥ 1 ug/ml				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Anti-PRP	Pn-Men	PII(M4)	128	117	91.4	85.1	95.6	71	55.5	46.4	64.3	1.349	1.019	1.785
		PIII(M5)	127	125	98.4	94.4	99.8	110	86.6	79.4	92.0	4.227	3.360	5.319
		Pre-Booster	122	104	85.2	77.7	91.0	38	31.1	23.1	40.2	0.550	0.432	0.701
		Post-Booster(M1)	127	127	100	97.1	100	126	99.2	95.7	100	33.487	27.109	41.365
		Post-Booster(36M of age)	118	118	100	96.9	100	92	78.0	69.4	85.1	2.506	1.990	3.157
		Post-Booster(48M of age)	123	122	99.2	95.6	100	83	67.5	58.4	75.6	1.939	1.562	2.407
		Post-Booster(72M of age)	127	126	99.2	95.7	100	85	66.9	58.0	75.0	1.655	1.339	2.045
	Pn-Neis	PII(M4)	137	133	97.1	92.7	99.2	105	76.6	68.7	83.4	2.593	2.056	3.271
		PIII(M5)	135	135	100	97.3	100	129	95.6	90.6	98.4	6.482	5.480	7.668
		Pre-Booster	126	111	88.1	81.1	93.2	42	33.3	25.2	42.3	0.627	0.501	0.785
		Post-Booster(M1)	134	134	100	97.3	100	134	100	97.3	100	36.349	30.215	43.729
		Post-Booster(36M of age)	130	130	100	97.2	100	101	77.7	69.6	84.5	2.288	1.837	2.851
		Post-Booster(48M of age)	128	127	99.2	95.7	100	80	62.5	53.5	70.9	1.782	1.420	2.235
		Post-Booster(72M of age)	134	132	98.5	94.7	99.8	77	57.5	48.6	66.0	1.647	1.298	2.090
	Pn-HibC	PII(M4)	131	123	93.9	88.3	97.3	89	67.9	59.2	75.8	1.993	1.525	2.606
		PIII(M5)	130	128	98.5	94.6	99.8	127	97.7	93.4	99.5	13.714	11.109	16.931
		Pre-Booster	122	117	95.9	90.7	98.7	70	57.4	48.1	66.3	1.251	0.988	1.583
		Post-Booster(M1)	130	130	100	97.2	100	130	100	97.2	100	90.530	75.726	108.229
		Post-Booster(36M of age)	121	121	100	97.0	100	113	93.4	87.4	97.1	4.213	3.405	5.213
		Post-Booster(48M of age)	122	122	100	97.0	100	110	90.2	83.4	94.8	3.757	3.029	4.659
		Post-Booster(72M of age)	130	130	100	97.2	100	110	84.6	77.2	90.3	2.947	2.396	3.624
	Pr-HibC	PII(M4)	131	123	93.9	88.3	97.3	79	60.3	51.4	68.7	1.609	1.214	2.135
		PIII(M5)	132	132	100	97.2	100	128	97.0	92.4	99.2	10.695	8.868	12.900
		Pre-Booster	124	120	96.8	91.9	99.1	60	48.4	39.3	57.5	0.852	0.697	1.040
		Post-Booster(M1)	130	130	100	97.2	100	130	100	97.2	100	65.650	52.762	81.687
		Post-Booster(36M of age)	125	125	100	97.1	100	106	84.8	77.3	90.6	3.773	3.039	4.685
		Post-Booster(48M of age)	125	124	99.2	95.6	100	99	79.2	71.0	85.9	2.803	2.274	3.456
		Post-Booster(72M of age)	132	132	100	97.2	100	100	75.8	67.5	82.8	2.558	2.065	3.168

Persistence of the antibodies of the concomitant vaccines (data not shown)

- For each of the common pneumococcal vaccine serotypes (4, 6B, 9V, 14, 18C, 19F and 23F), at least 81.5% of the subjects had antibody concentrations ≥ 0.05 µg/ml. The percentage of subjects with antibody concentrations ≥ 0.2 µg/ml was 25.2% for serotype 4 (Pn-Neis group) to 100% for serotype 14 (Pn-Men and Pr-HibC groups).
- For each of the 3 additional serotypes contained in Synflorix (1, 5 and 7F), at least 87.7% of the subjects of groups Pn-Men, Pn-Neis and Pn-HibC had antibody concentrations ≥ 0.05 µg/ml. The percentage of subjects with antibody concentrations ≥ 0.2 µg/ml was at least 41.5% in these three groups. For group Pr-HibC, the percentage of subjects with antibody concentrations ≥ 0.05 µg/ml range from 76.5% to 85.6% and between 25.0% and 43.9% of subjects had antibody concentrations ≥ 0.2 µg/ml.
- For each of the common pneumococcal vaccine serotypes, the GMCs ranged from 0.12 (anti-4 in group Pn-HibC) to 4.24 (anti-19F in group Pn-HibC). For each of the 3 additional serotypes contained in Synflorix (1, 5 and 7F), the GMCs varied between 0.19 (anti-1 in Pn-Men) and 0.64 (anti-7F in group Pn-HibC).

Discussion on clinical aspects

There are not any particular concerns raised by the new data provided. Five years postbooster vaccination, a progressive decrease in anti-PRP titres was observed and all subjects vaccinated with Menitorix had seroprotective titres against its Hib component. However, a sharp drop in the percentage of subjects with HPA rSBA-MenC titre ≥ 1:8 occurred between Year 3 and Year 5 due to the change of assay (from GSK to HPA), and therefore, no clear conclusion can be drawn.

Safety

There were no serious adverse events that were considered by the investigator to be possibly related to study vaccination or related to study participation or concomitant medication/vaccination and lack of vaccine efficacy during the persistence phase of the study.

Conclusion

Following the conclusion of the paediatric WS procedure UK/W/0028/pdWS/006 the applicant has submitted a variation to update section 5.1 of the SmPC with the long-term persistence data from study Hib-MenC-TT-035 M72. The applicant has also taken this opportunity to make minor corrections to other sections of the SmPC, the labelling and package leaflet.

The applicant has addressed the outstanding issue raised in the request for supplementary information.

The proposed changes to the SmPC, labelling and package leaflet are acceptable.

Based on the data submitted, there is no change to the positive benefit risk balance of Menitorix in the licensed indication.

Decision - Granted
Date - 29 February 2016