

ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, APPLICANTS AND MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Applicant	(Invented) Name	Strength *	Pharmaceutical form	Route of administration	Content (concentration)
United Kingdom	SmithKline Beecham PLC, 980 Great West Road, Brentford, Middlesex TW8 9GS United Kingdom		Menitorix	5 µg Hib PRP + 12.5 µg TT + 5 µg MenC PSC + 5 µg TT	powder and solvent for solution for injection	intramuscular injection	0.5ml
Belgium	GlaxoSmithkline Biologicals S.A., 89 rue de l'Institut, B-1330 Rixensart, Belgium		Menitorix	5 µg Hib PRP + 12.5 µg TT + 5 µg MenC PSC + 5 µg TT	powder and solvent for solution for injection	intramuscular injection	0.5 ml
Greece		GlaxoSmithkline A.E.B.E. 266 Leof. Kifisias, 152 32 Halandri Greece	Menitorix	5 µg Hib PRP + 12.5 µg TT + 5 µg MenC PSC + 5 µg TT	powder and solvent for solution for injection	intramuscular injection	0.5 ml
Ireland		GlaxoSmithKline (Ireland) Ltd. Stonemasons Way, Rathfarnham, Dublin 16 Ireland	Menitorix	5 µg Hib PRP + 12.5 µg TT + 5 µg MenC PSC + 5 µg TT	powder and solvent for solution for injection	intramuscular injection	0.5 ml
Poland		SmithKline Beecham plc 980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom	Menitorix	5 µg Hib PRP + 12.5 µg TT + 5 µg MenC PSC + 5 µg TT	powder and solvent for solution for injection	intramuscular injection	0.5 ml
Spain		GlaxoSmithKline, S.A Severo Ochoa, 2 Tres Cantos, Madrid Spain	Menitorix	5 µg Hib PRP + 12.5 µg TT + 5 µg MenC PSC + 5 µg TT	powder and solvent for solution for injection	intramuscular injection	0.5 ml

* Hib PRP - Haemophilus influenzae type B polyribosylribitol phosphate
TT - tetanus toxoid
MenC PSC - Neisseria meningitidis serogroup C polysaccharide

ANNEX II

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY
OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET
PRESENTED BY THE EMEA**

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF MENITORIX

Menitorix is a freeze-dried vaccine preparation consisting of 5µg of the purified *H. influenzae* type b capsular polysaccharide, polyribosylribitol phosphate (PRP) and 5µg of the meningococcal capsular polysaccharide of group C (PSC) both directly conjugated to tetanus toxoid (TT) carrier protein. The product is used for the active immunization of infants from the age of 2 months and toddlers up to the age of 2 years for the prevention of invasive diseases caused by *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* group C (MenC) and is administered by intramuscular injection.

The Applicant/MAH submitted an application for a Marketing Authorisation through the mutual recognition procedure for Menitorix on the basis of the marketing authorisation granted by the UK. The referral procedure was initiated with UK as the reference member state (RMS), due to concerns raised by the concerned member states Greece, Poland and Spain regarding major safety and efficacy issues and the immunological protection correlates, they considered the submitted clinical documentation insufficient to establish the clinical efficacy and safety of Menitorix, considering the product to be an entirely new conjugated, bivalent vaccine. These issues were referred to the CHMP during the referral procedure under Article 29 of Directive 2001/83/EC, as amended, on 26 April 2007.

Following the initial assessment, the CHMP considered that under the conditions of study, the safety and immunogenicity data provided were adequate to assess the risk-benefit relationship for the use of *Menitorix* for priming and/or boosting and could be used to assess the likely protection that will be afforded by the vaccine. The size of the safety database derived from clinical studies and the similarity of this new vaccine to already licensed products were both reasons to accept the database provided, which is supported by the fact that the available safety data do not indicate any unusual problems. However, the CHMP considered that there were concerns regarding the long-term antibody persistence, the adequacy of the safety data set in the light of the CHMP Guideline on Clinical Evaluation of New Vaccines, and the indication of Menitorix for both priming and boosting. The CHMP adopted a List of Outstanding Issues for the Applicant/MAH to address and requested the Vaccine Working Party (VWP) to consider the same outstanding issues. The VWP considered the new submitted data along with the already submitted data and agreed that the safety and immunogenicity data are adequate and satisfactory to support the approval of Menitorix. The data support the use of Menitorix for priming in infancy and for boosting in the second year of life and for boosting toddlers who have been primed with Menitorix or with other Hib and MenC conjugate vaccines.

In order to discuss the implication for long-term protection against MenC of the 18-month post booster data in study 022, in particular for those receiving primary vaccination with Menitorix, the Applicant/MAH reviewed the available data relating to antibody titres and vaccine effectiveness after the administration of a single dose of mono-component vaccines in the second year of life. The data from SPCs, literature and generated during clinical development combined with recent surveillance data from the United Kingdom and Canada suggest that vaccine effectiveness remained high in unprimed subjects who had been vaccinated in their second year of life with a single dose. Based on the SBA-MenC titres and SBA GMT obtained in studies and because of the effectiveness of single doses of mono-component MenC conjugate vaccines in unprimed toddlers, the Applicant/MAH concluded that the long-term efficacy of *Menitorix* will be at least as good, if not better, as that observed in this age group in the UK and Canada. An ongoing study will generate long-term SBA data while the Applicant/MAH also committed to monitor antibody persistence for five years in subsequent studies 023, 024, 025 and 026, in line with the "Note for guidance on clinical investigation of medicinal products in the paediatric population" (CPMP/ICH/2711/99).

The CHMP considered that the data suggests that the likely long term protection afforded by *Menitorix* should not be a cause for concern when used for priming and boosting or for boosting children primed with other MenC conjugate vaccines. Furthermore the CHMP considers that data on the persistence of SBA titres for up to 5 years after boosting with *Menitorix* alone cannot predict the

longer-term protective effect of vaccination, which can only be estimated by detailed surveillance of disease and therefore agrees with the proposed revised SPC which accurately and comprehensively reflects the extensive body of data that has already been accumulated with respect to the immunity afforded by this vaccine.

In order to further justify the adequacy of the safety database in children primed and/or boosted with *Menitorix*, the Applicant/MAH provided additional data from two recently reported studies, augmenting the total database with an additional 1131 subjects who received a total of 2992 doses of *Menitorix*. The new totals are therefore 3293 infants vaccinated with *Menitorix* either as a primary course or as a booster and 578 infants vaccinated with 1713 doses of closely related Hib-MenC formulations. The incidence of grade 3 unsolicited symptoms considered to be related to vaccination or booster vaccination in the previously submitted data was very low and similar between study groups. The two new studies provided similar data. *Menitorix* has been used in UK since September 2006 and three 6-monthly PSURs have been issued to date, with reassuringly low reporting rates and no new safety concerns allowing the Applicant/MAH to conclude that the safety profile is adequately reflected in the Core Safety Information. However, following several reports of suspected ADRs, section 4.8 of the *Menitorix* SPC was updated. The Applicant/MAH considers that the extent of the total safety database is entirely consistent with the recommendations of the CHMP *Guideline on Clinical Evaluation of New Vaccines* and is sufficiently large to identify uncommon events.

The CHMP considered that the safety data submitted indicates that the local and systemic AEs observed during clinical studies were as expected in terms of types and rates for a polysaccharide-protein conjugate vaccine and showed similar reactogenicity to other mono-component MenC and Hib vaccines in various clinical studies. The post-marketing data raised no new concerns and the satisfactory safety profile of the vaccine was supported by the safety data reported in PSUR 3 from use of *Menitorix* in approximately 0.6 million toddlers as a booster dose for Hib and MenC in the UK. Therefore, the CHMP considered that the size of the safety database was already satisfactory before provision of the additional clinical study data and that the new information submitted brings the total to well above the minimum suggested in the CHMP guideline. Overall, the CHMP considers the safety database to be of adequate size and satisfactory in content, supporting the use of *Menitorix* for priming in infancy and for boosting children in the second year of life who have been primed with *Menitorix* or with other Hib and MenC conjugate vaccines.

Efficacy and Safety conclusions

The immunogenicity data indicates that *Menitorix* will be at least as effective as the licensed PRP-T and MenC conjugate vaccines when used for priming and/or for boosting in accordance with the SPC. *Menitorix* can be used to boost toddlers primed with this vaccine or with other licensed Hib and MenC conjugate vaccines. The CHMP considers that under the conditions of study, *Menitorix* elicits sufficient immune responses to both conjugate components to provide protection that is expected to be at least as good as that of licensed comparators. The Company has already planned to assess long-term antibody persistence and, to complete this procedure, should formally commit to providing to the relevant national competent authorities for assessment the data from longer-term follow-up of studies 010/022 and 013 with anticipated timelines.

The total safety database derived from clinical studies now consists of 3293 infants vaccinated with *Menitorix* either as a primary course or as a booster and 578 infants vaccinated with 1713 doses of closely related Hib-MenC formulations and therefore exceeds that suggested by the CHMP Guideline for truly new vaccines. The similarity of *Menitorix* to already licensed products and the fact that the available safety data do not indicate any unusual problems are both reasons to accept the database provided. *Menitorix*-containing regimens were not more reactogenic than the comparative regimens in which the same total range of antigens was administered. Finally, the post-marketing surveillance data from the UK are reassuring. The safety and immunogenicity data provided are adequate to establish that the risk-benefit relationship for the use of *Menitorix* for priming in infancy and/or boosting in the second year of life is favourable. The most recent updates to the SPC serve to reflect the total data available thus far.

In line with these conclusions, the CHMP regarded Menitorix (GSK Bio) as acceptable for registration.

Based on

- the Rapporteur's and Co-Rapporteur's assessment reports,
- the Applicant/MAH response to the CHMP questions,
- the Scientific discussion within the Committee,

the CHMP has recommended granting the Marketing Authorisation for Menitorix, with amendments to the relevant sections of the PI and with commitments to be fulfilled. The revised Product Information (Summary of Product Characteristics, Labelling and Package Leaflet) is set out in Annex II of the Opinion. The conditions of the Marketing Authorisation are set out in Annex IV.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Menitorix and associated names (see Annex I) powder and solvent for solution for injection
Haemophilus type b and *Meningococcal* group C conjugate vaccine
[See Annex I – To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, each 0.5 ml dose contains:

Haemophilus type b polysaccharide (polyribosylribitol phosphate)	5 micrograms
conjugated to tetanus toxoid as carrier protein	12.5 micrograms
<i>Neisseria meningitidis</i> serogroup C (strain C11) polysaccharide	5 micrograms
conjugated to tetanus toxoid as carrier protein	5 micrograms

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL form

Powder and solvent for solution for injection
White powder and a clear colourless solvent.

4. Clinical particulars

4.1 Therapeutic indications

Active immunization of infants from the age of 2 months and toddlers up to the age of 2 years for the prevention of invasive diseases caused by *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* group C (MenC).

See also section 4.4.

4.2 Posology and method of administration

Primary vaccination in infants from 2 months 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.

There are no data on the use of Menitorix for one or two doses of the primary vaccination course and other Hib and/or MenC conjugate vaccines for other dose(s). It is recommended that infants who receive Menitorix for the first dose should also receive this vaccine for the second and third doses of the primary vaccination course.

Booster vaccination:

After primary vaccination in infancy, booster doses of Hib and MenC must be administered. In children who received an acellular pertussis combination vaccine containing Hib in the primary infant immunisation series the Hib booster dose should be given before the age of 2 years.

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. 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.

Menitorix is not recommended for use in children above 2 years of age due to a lack of data on safety and efficacy.

Long-term immunogenicity data following the use of Menitorix as a primary and booster vaccination are not yet available (see section 5.1).

Menitorix should be given by 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. (see also sections 4.4 and 4.5)

Menitorix should under no circumstances be administered intravascularly, intradermally or subcutaneously.

4.3 Contraindications

Hypersensitivity to the active substances, including tetanus toxoid, or to any of the excipients (see sections 2 and 6.1).

Hypersensitivity reaction after previous administration of Menitorix.

Acute severe febrile illness. The presence of a minor infection is not a contraindication for vaccination.

4.4 Special warnings and precautions for use

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

Vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

The vaccine should be given with caution to individuals with thrombocytopenia or any coagulation disorder. No data are available on subcutaneous administration of Menitorix, therefore the possibility of any toxicity or reduced efficacy that might occur with this route of administration is unknown.

Menitorix will only confer protection against *Haemophilus influenzae* type b and *Neisseria meningitidis* group C. As for any vaccine, Menitorix may not completely protect against the infections it is intended to prevent in every vaccinated individual

There are no data available on administration of Menitorix in toddlers not already primed with Hib and MenC conjugates.

No data are available on the use of Menitorix in immunodeficient subjects. In individuals with impaired immune responsiveness (whether due to the use of immunosuppressive therapy, a genetic defect, human immunodeficiency virus (HIV) infection, or other causes) a protective immune response to Hib and MenC conjugate vaccines may not be obtained. Individuals with complement deficiencies and individuals with functional or anatomical asplenia may mount an immune response to Hib and MenC conjugate vaccines; however the degree of protection that would be afforded is unknown.

There are no data available on the use of Menitorix in infants who were born prematurely. Therefore the degree of protection that would be afforded is unknown.

Although symptoms of meningism such as neck pain/stiffness or photophobia have been reported following administration of other MenC conjugate vaccines, there is no evidence that MenC conjugate vaccines cause meningitis. Clinical alertness to the possibility of co-incidental meningitis should be maintained.

Immunisation with this vaccine does not substitute for routine tetanus immunisation.

Since Hib capsular polysaccharide antigen is excreted in the urine, a positive urine antigen test can be observed within 1-2 weeks following vaccination. Other diagnostic tests, not based on the detection of the capsular antigen in urine, should be used to confirm Hib disease during this period.

4.5 Interaction with other medicinal products and other forms of interaction

Menitorix must not be mixed with any other vaccine in the same syringe.

Different injectable vaccines should always be given at different injection sites.

In various studies with licensed monovalent meningococcal group C conjugate vaccines, concomitant administration with combinations containing diphtheria, tetanus and acellular pertussis components (with or without inactivated polio viruses, hepatitis B surface antigen or Hib conjugate [e.g. DTPa-HBV-IPV-Hib*]), has been shown to result in lower serum bactericidal antibody (SBA) geometric mean titres (GMT) compared to separate administrations or to co-administration with whole cell pertussis vaccines. The proportions reaching SBA titres of at least 1:8 are not affected. At present, the potential implications of these observations for the duration of protection are not known.

In clinical trials of primary vaccination series, Menitorix was administered concomitantly (into opposite thighs) with a DTPa-HBV-IPV vaccine. Responses to all the co-administered antigens were satisfactory and were similar to those achieved in control groups that received DTPa-HBV-IPV-Hib* concomitantly with a MenC conjugate vaccine (MenCC) or DTPa-HBV-IPV* concomitantly with a Hib conjugate vaccine and no MenCC. The immune response to the Hib and MenC components of Menitorix was only assessed in primary vaccination clinical studies that employed co-administration with DTPa-IPV* or DTPa-HBV-IPV* vaccines.

In a trial of primary vaccination, concomitant administration of an investigational vaccine containing the same amount of conjugated Hib and MenC saccharides as in Menitorix with DTPa-HBV-IPV* and a licensed pneumococcal saccharide conjugated vaccine (the three injections were made into anatomically distant sites) gave similar immune responses to the seven pneumococcal serotypes as achieved in a group that received DTPa-HBV-IPV* concomitantly with Hib (conjugated to tetanus toxoid) and a licensed pneumococcal saccharide conjugated vaccine.

There are no data on concomitant use of Menitorix with whole cell pertussis and oral poliomyelitis vaccines, however, no interference is expected.

In a trial of booster vaccination against Hib and MenC, Menitorix was administered concomitantly (into opposite thighs) with a first dose of combined measles, mumps and rubella (MMR) vaccine. Compared to the two control groups that received either Menitorix or MMR alone the immune responses to the antigens in both vaccines were not affected by concomitant administration. See sections 4.8 and 5.1.

*GlaxoSmithKline combination vaccine

4.6 Pregnancy and lactation

Menitorix is not intended for use in adults. Information on the safety of the vaccine when used during pregnancy or lactation is not available.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

- Clinical trials

In clinical trials, Menitorix was administered as a 3-dose primary series (N=1,171) or as a booster (N=991) dose. When Menitorix was administered as a 3-dose primary vaccination course, a DTPa-HBV-IPV* vaccine (N=796) or a DTPa-IPV vaccine* (N=375) was administered concomitantly. Adverse reactions occurring during these studies were mostly reported within 48 hours following vaccination.

In two clinical trials (N=578), Menitorix was administered concomitantly with Measles, Mumps, Rubella (MMR) vaccine. In one of these trials, the incidences of adverse reactions observed in subjects (N=102) who received Menitorix concomitantly with MMR* were similar to those observed in the group who received MMR alone (N=91) or Menitorix alone (N=104). (See sections 4.5 and 5.1)

Adverse reactions considered as being at least possibly related to vaccination have been categorised by frequency as follows.

Very common ($\geq 1/10$)

Common ($\geq 1/100, < 1/10$)

Uncommon ($\geq 1/1,000, < 1/100$)

Rare ($\geq 1/10,000, < 1/1,000$)

Very rare ($< 1/10,000$),

not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Psychiatric disorders:

very common: irritability

uncommon: crying

Nervous system disorders:

very common: drowsiness

Gastrointestinal disorders:

very common: appetite lost

uncommon: diarrhoea, vomiting

Skin and subcutaneous tissue disorders:

uncommon: dermatitis atopic

rare: rash

General disorders and administration site conditions:

very common: fever (rectal $\geq 38^\circ\text{C}$), swelling, pain, redness common: injection site reaction

uncommon: fever (rectal $> 39.5^\circ\text{C}$), malaise

- Post-marketing experience

The following adverse events have been reported after administration of Menitorix:

Allergic reactions (including urticaria and anaphylactoid reactions), lymphadenopathy, dizziness, febrile seizures, hypotonia, headache.

- Other possible side effects:

The following have not been reported in association with administration of Menitorix but have occurred very rarely during routine use of licensed meningococcal group C conjugate vaccines:

Severe skin reactions, collapse or shock-like state (hypotonic-hyporesponsiveness episode), faints, seizures in patients with pre-existing seizure disorders, hypoaesthesia, paraesthesia, relapse of nephrotic syndrome, arthralgia, petechiae and/or purpura.

*GlaxoSmithKline combination vaccine

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: bacterial vaccines ATC code: J07AG53

Primary vaccination course

Clinical trials have evaluated the antibody responses at one month after two doses and after completion of a 3-dose primary vaccination course of Menitorix (co-administered with DTPa-HBV-IPV or DTPa-IPV vaccines) given at approximately 2, 3, 4 months or 2, 4, 6 months to 814 infants.

Percentages of subjects with antibody titres \geq assay cut-off one month after primary vaccination with Menitorix co-administered with DTPa-IPV* or DTPa-HBV-IPV* vaccines were as follows:

Antibody		2-3-4 month schedule	
		After two doses N=93	After three doses N=330†
Anti-PRP	≥ 0.15 micrograms/ml	96.8%	100.0%
	≥ 1 micrograms/ml	76.3%	97.3%
	GMC (micrograms/ml)	3.40	11.18
rSBA-MenC	$\geq 1:8$	100.0%	98.8%
	$\geq 1:32$	98.9%	97.9%
	$\geq 1:128$	98.9%	92.4%
	GMT	679.6	685.5

N= number of subjects with available results

%= percentage of subjects with titres equal to or above the cut-off

PRP= polyribosylribitol phosphate

rSBA-MenC= serum bactericidal antibodies against meningococcal polysaccharide C using rabbit complement

GMC or GMT= geometric mean antibody concentration or titre

†= subjects ≤ 18 weeks of age at time of third Menitorix dose

Antibody		2-4-6 month schedule	
		After two doses N=111	After three doses N=111
Anti-PRP	≥0.15 lmicrograms/ml	96.4%	100.0%
	≥1 micrograms/ml	74.8%	97.3%
	GMC (micrograms/ml)	3.26	12.84
rSBA-MenC	≥1:8	100.0%	100.0%
	≥1:32	100.0%	100.0%
	≥1:128	96.4%	99.1%
	GMT	847.2	2467.1

N= number of subjects with available results

%= percentage of subjects with titres equal to or above the cut-off

PRP= polyribosylribitol phosphate

rSBA-MenC= serum bactericidal antibodies against meningococcal polysaccharide C using rabbit complement

GMC or GMT= geometric mean antibody concentration or titre

Antibody persistence has been demonstrated for Hib in three clinical trials (N=217) with 98.2% of subjects having an anti-PRP concentration of ≥ 0.15 micrograms/ml at 11-18 months of age i.e. at 7-14 months following completion of a 3-dose primary series with Menitorix.

In three clinical trials (N=209), 92.3% of subjects had an SBA-MenC titre ≥ 1/8 at 11–18 months of age, i.e. at 7-14 months following completion of a 3-dose primary series with Menitorix. All subjects responded immunologically to a challenge dose of 10 µg of unconjugated group C meningococcal polysaccharide with a thirty-three-fold increase in SBA titres demonstrating the immune memory induced by the primary vaccination course.

Booster vaccination

Percentages of subjects with antibody titres ≥ assay cut-off one month after booster vaccination with Menitorix administered alone or co-administered with DTPa-HBV-IPV* vaccine were as follows:

	Primary vaccination history		
	Subjects primed with 3 doses of Menitorix* N=123	Subjects primed with 2 doses of NeisVac-C** N=167	Subjects primed with 3 doses of Meningitec** or Menjugate** N=96
Anti-PRP antibodies			
≥0.15 micrograms/ml	100.0%	100.0%	100.0%
≥1 micrograms/ml	100.0%	98.8%	99.0%
GMC (micrograms/ml)	56.72	77.15	30.27
rSBA-MenC			
≥1:8	100.0%	99.4%	98.9%
≥1:32	100.0%	99.4%	97.9%
≥1:128	99.2%	99.4%	92.6%
GMT	4172.5	11710.5	685.0

N= number of subjects with available results

PRP= polyribosylribitol phosphohate

rSBA-MenC= serum bactericidal antibodies against meningococcal polysaccharide C using rabbit complement

GMC or GMT= geometric mean antibody concentration or titre

%= percentage of subjects with titres equal to or above the cut-off

*= co-administered with DTPa-HBV-IPV

**= co-administered with DTPa-Hib-TT containing vaccines

Percentages of subjects with antibody titres \geq assay cut-off one month after booster vaccination with Menitorix co-administered with measles-mumps-rubella vaccine (MMR)* were as follows:

Primary vaccination history			
	Subjects primed with 3 doses of Menitorix* N= 349	Subjects primed with 3 doses of Meningitec + Pediacel N= 115	Subjects primed with 3 doses of licensed Meningitec** or Menjugate** N= 96
Anti-PRP antibodies			
≥ 0.15 micrograms/ml	100%	100%	100%
≥ 1 micrograms/ml	100%	100%	97.9%
GMC (micrograms/ml)	93.19	44.27	37.17
rSBA-MenC			
$\geq 1:8$	99.1%	95.6%	98.9%
$\geq 1:32$	98.8%	94.7%	96.8%
$\geq 1:128$	97.7%	86.0%	89.5%
GMT	2193.7	477.9	670.2

N= number of subjects with available results

PRP= polyribosylribitol phosphohate

rSBA-MenC= serum bactericidal antibodies against meningococcal polysaccharide C using rabbit complement

GMC or GMT= geometric mean antibody concentration or titre

%= percentage of subjects with titres equal to or above the cut-off

*= co-administered with DTPa-IPV vaccines

**= co-administered with DTPa-Hib-TT containing vaccines

Antibody levels have been measured at 18 months after the administration of a booster dose of Menitorix at age 14 Months to subjects who had been primed in infancy with either Menitorix at 2, 4 and 6 months of age or with NeisVac-C at 2, 4 months of age (and a DTPa/Hib containing vaccine at 2, 4, 6 months of age). SBA-MenC results are available for 177 subjects, anti-PRP results for 178 subjects. Overall, 92.7% of 177 subjects had SBA-MenC titres of at least 1:8 and 99.4% of the 178 subjects had anti-PRP antibody concentrations of at least 0.15 $\mu\text{g/ml}$. In the Menitorix primed and boosted group 49/56 (87.5%) of the subjects had SBA-MenC titers of at least 1:8 and 56/56 (100%) had anti-PRP antibody concentrations of at least 0.15 $\mu\text{g/ml}$. In the group primed with NeisVac-C 115/121 (95%) had SBA-MenC titers of at least 1:8 and 121/122 (99.2%) had anti-PRP antibody concentrations of at least 0.15 $\mu\text{g/ml}$. There were no significant differences between the two groups in the proportions with SBA-MenC titers of at least 1:8 or anti-PRP antibody concentrations of at least 0.15 $\mu\text{g/ml}$.

Estimates of vaccine effectiveness from the UK's routine immunisation programme (using various quantities of three meningococcal group C conjugate vaccines) covering the period from introduction at the end of 1999 to March 2004 have demonstrated the need for a booster dose after completion of the primary series (three doses administered at 2, 3 and 4 months). Within one year of completion of

the primary series, vaccine effectiveness in the infant cohort was estimated at 93% (95% confidence intervals 67-99%). However, more than one year after completion of the primary series, there was clear evidence of waning protection. Estimates of effectiveness based on a small number of cases to date indicate that there may also be waning protection in children who received a single priming dose as toddlers. Effectiveness in all other age groups (up to 18 years) primed with a single dose has so far remained around 90% or more within and more than one year after vaccination.

*GlaxoSmithKline combination vaccine

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and single and repeated dose toxicity studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Trometamol

Sucrose

Solvent:

Sodium chloride

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

After reconstitution, the vaccine should be administered promptly or kept in the refrigerator (2°C – 8°C). If it is not used within 24 hours, it should be discarded.

Experimental data show that the reconstituted vaccine could also be kept to 24 hours at ambient temperature (25°C). If it is not used within 24 hours, it should be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Do not freeze

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Powder in a vial (type I glass) with a stopper (butyl rubber),
0.5 ml of solvent in a pre-filled syringe (type I glass) with a plunger stopper (butyl rubber) with or without separate needles in the following pack sizes:

- pack size of 1 vial of powder plus 1 pre-filled syringe of solvent with 2 separate needles or without needles
- pack size of 10 vials of powder plus 10 pre-filled syringes of solvent with 2 separate needles or without needles

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of physical aspect prior to administration. In the event of either being observed, discard the vaccine.

The vaccine must be reconstituted by adding the entire contents of the pre-filled syringe of solvent to the vial containing the powder. After the addition of the solvent, the mixture should be well shaken until the powder is completely dissolved in the solvent.

The reconstituted vaccine is a clear and colourless solution. Inject the entire contents of the vial.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Menitorix and associated names (See Annex I) powder and solvent for solution for injection
Haemophilus type b and *Meningococcal* group C conjugate vaccine
[See Annex I – To be completed nationally]

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1 dose (0.5 ml) contains:

<i>Haemophilus</i> type b polysaccharide (polyribosylribitol phosphate)	5 micrograms
conjugated to tetanus toxoid as carrier protein	12.5 micrograms
<i>Neisseria meningitidis</i> serogroup C (strain C11) polysaccharide	5 micrograms
conjugated to tetanus toxoid as carrier protein	5 micrograms

3. LIST OF EXCIPIENTS

Powder:

Trometamol
Sucrose

Solvent:

Sodium chloride
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 vial: Powder
1 pre-filled syringe: Solvent
1 dose (0.5 ml)

1 vial: Powder
1 pre-filled syringe: Solvent
2 needles
1 dose (0.5 ml)

10 vials: Powder
10 pre-filled syringes: Solvent
10 x 1 dose (0.5 ml)

10 vials: Powder
10 pre-filled syringes: Solvent
20 Needles
10 x 1 dose (0.5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Read the package leaflet before use
Shake well before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not inject intravenously.

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED SYRINGE**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Menitorix and associated names (see Annex I) solvent for solution for injection [See Annex I – To be completed nationally]

I.M.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

LOT:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 ml)

6. OTHER

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Menitorix and associated names (See Annex I) powder for solution for injection
Haemophilus type b and Meningococcal group C conjugate vaccine
[See Annex I – To be completed nationally]
I.M.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

LOT:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Menitorix and associated names (See Annex I) powder and solvent for solution for injection

[See Annex I – To be completed nationally]

Haemophilus type b and *Meningococcal* group C conjugate vaccine

Read all of this leaflet carefully before your child starts receiving this vaccine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This vaccine has been prescribed for your child. Do not pass it on to others.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Menitorix is and what it is used for
2. Before your child receives Menitorix
3. How Menitorix is given
4. Possible side effects
5. How to store Menitorix
6. Further information

1. WHAT MENITORIX IS AND WHAT IT IS USED FOR

Menitorix is a vaccine that can be given to children after the age of 2 months up to 2 years to prevent infectious diseases caused by *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* group C (MenC) bacteria. The vaccine works by causing the body to produce its own protection (antibodies) against these bacteria. The vaccine cannot cause Hib and MenC.

- ***Haemophilus influenzae* type b (Hib):** Hib bacteria most frequently cause meningitis (inflammation of the coverings of the brain and spinal cord). Even after recovery from Hib meningitis there can be complications such as mental retardation, spastic paralysis, deafness or epilepsy. Hib infection can also cause a life-threatening inflammation of the throat with severe swelling that can cause suffocation. Less commonly, the bacteria can infect other parts of the body, particularly the lungs (causing pneumonia) and the bones and joints.
- ***Neisseria meningitidis* group C (MenC):** Like Hib bacteria, MenC bacteria most frequently cause meningitis. They may also cause severe blood infections and spread throughout the body.

Vaccination is the best way to protect against diseases caused by these bacteria. Remember, however, that 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.

2. BEFORE YOUR CHILD RECEIVES MENITORIX

Menitorix should not be given:

- if your child has previously had any allergic reaction to Menitorix, to any Hib or MenC vaccine, to tetanus toxoid or to any other ingredient present in the vaccine (see section 6). Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

- if your child has a high temperature (38°C or above) or a severe infection. It is usual to wait until the child is better before giving the vaccine. A minor infection such as a cold should not be a problem but talk to your doctor or nurse first.

Remember that the first dose of Menitorix should not be given before your child is 2 months of age.

Take special care with Menitorix:

- if your child has a bleeding problem or bruises easily.
- if your child takes medicines or has any treatment which may affect the immune system. Also, if your child has HIV infection or any other illness that can reduce his or her immunity to infections. Your child can still be given Menitorix if your doctor or nurse advises it but your child may not develop as good protection against Hib and MenC infections as other children.
- if your child was born prematurely (before 37 weeks). Menitorix can be given from the age of 2 months after birth onwards but it is not known if protection against Hib and MenC will be as good as in children born at term.

In the first 1-2 weeks after a dose of Menitorix it is possible that urine tests to detect Hib infection could give the wrong (false positive) results.

Using other medicines or vaccines

Please tell your doctor if your child is taking or has recently taken any other medicines, including medicines obtained without a prescription or has recently received any other vaccine.

Menitorix can be given at the same time as vaccines intended to protect against one or more of diphtheria, tetanus, whooping cough, polio, hepatitis B, pneumococcal conjugate vaccine and combined vaccines against measles, mumps and rubella (MMR). Any other vaccines that are given at the same time as Menitorix will be injected separately at different parts of the body.

Although Menitorix contains tetanus toxoid (inactivated bacterial toxin), which is used to immunise people against tetanus (lockjaw), it is still necessary that your child should receive the recommended childhood vaccinations against tetanus.

3. HOW MENITORIX IS GIVEN

Each dose of Menitorix is a single injection of half a millilitre (0.5 ml). The nurse or doctor will give Menitorix as an injection into the muscle (usually into the thigh muscle but in toddlers the arm muscle can be used) and will make sure that the vaccine is not given into a blood vessel or into the upper layer of the skin.

If Menitorix is used in infants for the first vaccinations against Hib and MenC:

Your child will receive three doses of Menitorix. The first dose should not be given before the age of 2 months and there should be a gap of at least four weeks between injections.

If Menitorix is used to boost protection against Hib and MenC:

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 can be used to boost protection in children who received Menitorix previously or in children who previously received other vaccines against these diseases (including children who received two doses of a MenC vaccine in early life).

If your child receives more Menitorix than he/she should

It is very unlikely that your child will receive too much or too little vaccine because each dose is provided in a separate vial and the vaccine is given by a doctor or nurse. If you are concerned about the dose or doses that have been given, please talk to your doctor or nurse.

If you forget to take your child for vaccination with Menitorix

Your doctor or nurse will advise when your child should attend for these injections. If you miss an appointment, it is very important that you contact the surgery or clinic and make a new appointment for your child to have the missed dose or doses as soon as possible.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Menitorix can cause side effects, although not everybody gets them.

Severe allergic reactions can occur to any vaccine but they are very rare and are usually seen in less than 1 in 10,000 people who are vaccinated. Your child may be asked to stay in the surgery or vaccination area for a short time after vaccination to check that he or she does not have an immediate allergic reaction. Tell the doctor or nurse immediately if your child develops a rash (which may be raised or lumpy), tightness of the throat, swelling of the face or neck or shortness of breath. Other possible symptoms of a severe allergic reaction include a drop in blood pressure and unconsciousness. It is very important that your child has immediate medical treatment for any severe allergic reaction. If the symptoms start after you have left the clinic, you should get medical help as soon as possible (for example, go to the nearest accident and emergency department).

In clinical trials that involved giving Menitorix for the first vaccinations against Hib and MenC or to boost protection against these diseases the side effects that occurred after vaccination were:

- ◆ **Very common (in more than 1 per 10 doses of vaccine)**
 - Pain, redness or swelling at the site of the injection
 - Fever (temperature of 38°C or above)
 - Irritability
 - Loss of appetite
 - Sleepiness

- ◆ **Uncommon (in less than 1 per 100 but more than 1 per 1,000 doses of vaccine)**
 - Crying
 - Diarrhoea
 - Being sick
 - Generally feeling unwell
 - Fever of 39.5°C or above

- ◆ **Rare (in less than 1 per 1,000 but more than 1 per 10,000 doses of vaccine)**
 - Rash

Other side effects which have occurred very rarely (in less than 1 per 10,000 doses of vaccine) in the days or weeks after vaccination with Menitorix include:

Allergic reactions (these can be recognised by itchy rash of the hands and feet, swelling of the eyes and face, difficulty in breathing or swallowing), swelling of the glands, dizziness, convulsions (fits) with high temperature, unusual muscle slackness, headache.

Some other side effects have been reported very rarely (in less than 1 per 10,000 doses of vaccine) in children who have received other MenC containing vaccines. They include: Collapse or shock, the child not responding to his or her parents for a time after vaccination, fainting, convulsions in

children who have had them before, lack of sensation or an increased sensation (for example pain, pins and needles or itching at the injection site), joint pain, or purple spots or patches under the skin.

This vaccine cannot cause MenC or Hib infections. If your child experiences neck pain, neck stiffness or a dislike of light (photophobia), drowsiness or confusion, or red or purple bruise-like spots that do not fade under pressure you should contact your doctor or local accident and emergency department immediately to rule out other causes.

If you have previously been told by your doctor that your child suffers from nephrotic syndrome (a kidney disease which may result in swelling, particularly around the face or eyes, protein in the urine making it appear frothy and/or weight gain) there may be an increased chance that this condition will reoccur within a few months after vaccination. You should tell your doctor if you notice similar symptoms in your child after vaccination.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE MENITORIX

Keep out of the reach and sight of children.

Do not use Menitorix after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Store in the original package in order to protect from light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Menitorix contains

- The active substances are:

<i>Haemophilus</i> type b polysaccharide (polyribosylribitol phosphate)	5 micrograms
conjugated to tetanus toxoid as carrier protein	12.5 micrograms
<i>Neisseria meningitidis</i> serogroup C (strain C11) polysaccharide	5 micrograms
conjugated to tetanus toxoid as carrier protein	5 micrograms

- The other ingredients are:

<u>Powder</u> : trometamol, sucrose
<u>Solvent</u> : sodium chloride, water for injections.

What Menitorix looks like and contents of the pack

Menitorix is supplied as a white powder of Hib-MenC vaccine in a glass vial, together with half a millilitre (0.5 ml) of clear colourless sodium chloride solvent in a pre-filled syringe for a 1 dose vaccine. This powder is dissolved in the solvent provided, just before injection.

Menitorix is available in packs of 1 or 10 with 2 separate needles or without needles.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

[See Annex I – To be completed nationally]

Manufacturer

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart
Belgium

This medicinal product is authorised in the Member States of the EEA under the following names:

United Kingdom

Menitorix

This leaflet was last approved in {MM/YYYY}

[To be completed nationally]

Detailed information on this medicine is available on the web site of:

[To be completed nationally]

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The following information is intended for medical or healthcare professionals only:

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of physical aspect prior to administration. In the event of either being observed, discard the vaccine.

The vaccine must be reconstituted by adding the entire contents of the pre-filled syringe of solvent to the vial containing the powder. After the addition of the solvent, the mixture should be well shaken until the powder is completely dissolved in the solvent.

Inject the entire contents of the vial.

After reconstitution, the vaccine should be administered promptly or kept in the refrigerator (2°C – 8°C). If it is not used within 24 hours, it should be discarded.

Experimental data show that the reconstituted vaccine could also be kept to 24 hours at ambient temperature (25°C). If it is not used within 24 hours, it should be discarded.

Any unused product or waste material should be disposed of in accordance with local requirements.

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATION

The National Competent Authorities, coordinated by the Reference Member State, shall ensure that the following conditions are fulfilled by the Marketing Authorisation Holders:

The Applicant/MAH is requested to commit to submitting for assessment, to the relevant national competent authorities, the results from the long-term antibody persistence data from the ongoing studies with *Menitorix* i.e. subjects from booster studies 013 and 022 are being followed up for antibody persistence as follows:

- Over 4 years of follow up of subjects from study 013 in studies 027, 028 and 029.
- Five years follow-up from 010/022 in subsequent studies 023, 024, 025 and 026.