Safeguarding public health

MHRA

Public Assessment Report

De-Centralised Procedure

Meningitec
Meningococcal serogroup C oligosaccharide conjugate vaccine (adsorbed)

UK/H/0356/02/DC

UK licence no: PL 00011/0496

John Wyeth & Brother Limited

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Module 1

Product Name	Meningitec Meningococcal serogroup C oligosaccharide conjugate vaccine (adsorbed)
Type of Application	Full dossier, Article 8.3(i), known active substance
Active Substance	Meningococcal serogroup C oligosaccharide CRM 197 conjugate vaccine (adsorbed)
Form	Suspension for injection in a pre-filled syringe
Strength	10 micrograms saccharide, approximately 15 micrograms CRM 197
MA Holder	John Wyeth & Brother Limited
RMS	UK
CMS	AT, BE, DE, DK, EL, ES, FI, FR, IE, IS, IT, LU, NL, NO, PT and SE
Procedure Number	UK/H/0356/02/DC
Timetable	Day 90 – 28th August 2007

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Meningitec suspension for injection in pre-filled syringe
Meningococcal serogroup C oligosaccharide conjugate vaccine (adsorbed).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5ml) contains:
Neisseria meningitidis (strain C11)
Serogroup C oligosaccharide…… 10 micrograms
Conjugated to *Corynebacterium diphtheriae*
CRM_{197} carrier protein……approximately 15 micrograms
Adsorbed on aluminium phosphate … 0.125 mg Al^{3+}

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection, in pre-filled syringe. After shaking, the vaccine is a homogeneous, white suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Active immunisation of children from 2 months of age, adolescents and adults for the prevention of invasive disease caused by *Neisseria meningitidis* serogroup C.

The use of Meningitec should be determined on the basis of official recommendations.

4.2 Posology and method of administration

Posology

There are no data on the use of different Meningococcal serogroup C conjugate vaccines within the primary series or for boosting. Whenever possible, the same vaccine should be used throughout.

Primary immunisation

Infants up to the age of 12 months: two doses, each of 0.5 mL, the first dose given not earlier than 2 months of age and with an interval of at least 2 months between doses.
Children over the age of 12 months, adolescents and adults: a single dose of 0.5 mL.
The timing of the doses should be in accordance with official recommendations.

Booster doses

It is recommended that a booster dose should be given after completion of the primary immunisation series in infants. The timing of this dose should be in accordance with available official recommendations. Information on responses to booster doses and on co-administration with other childhood vaccines is given in sections 5.1 and 4.5, respectively.

The need for booster doses in subjects primed with a single dose (i.e. aged 12 months or more when first immunised) has not yet been established.

Method of administration

Meningitec is for intramuscular injection, preferably in the anterolateral thigh in infants and in the deltoid region in older children, adolescents and adults. Meningitec should not be injected in the gluteal area.
Avoid injection into or near nerves and blood vessels.

The vaccine must not be administered intradermally, subcutaneously or intravenously (see section 4.4).

Separate injection sites should be used if more than one vaccine is being administered (see section 4.5). This vaccine must not be mixed with other vaccines in the same syringe.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients.
- Hypersensitivity to any vaccine containing diphtheria toxoid or non-toxic diphtheria toxin protein.
- Hypersensitivity after previous administration of Meningitec.
- As with other vaccines, the administration of Meningitec should be postponed in subjects suffering from an acute severe febrile illness.

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 anaphylactoid/anaphylactic event following the administration of the vaccine (see section 4.8 Undesirable effects).
As with any intramuscular injection, the vaccine should be given with caution to individuals with thrombocytopenia or any coagulation disorder or to those receiving anticoagulation therapy.

Meningitec will only confer protection against serogroup C of *Neisseria meningitidis* and may not completely prevent meningococcal serogroup C disease. It will not protect against other groups of *Neisseria meningitidis* or other organisms that cause meningitis or septicaemia. In the event of petechiae and/or purpura following vaccination (see section 4.8), the aetiology should be thoroughly investigated. Both infective and non-infective causes should be considered.

Although symptoms of meningism such as neckpain/stiffness or photophobia have been reported there is no evidence that the vaccine causes meningococcal C meningitis. Clinical alertness to the possibility of co-incidental meningitis should therefore be maintained.

Consideration should be given to the risk of *Neisseria meningitidis* serogroup C disease in a given population and the perceived benefits of immunisation before the institution of a widespread immunisation programme.

No data on the applicability of the vaccine to outbreak control are available.

The safety and immunogenicity have not been established in infants below the age of two months (see section 5.1 pharmacodynamic properties).

There are limited data on safety and immunogenicity of the vaccine in the adult population and there are no data in adults aged 65 years and older (see section 5.1).

Limited data are available on the use of Meningitec 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) the expected immune response to meningococcal serogroup C conjugate vaccines may not be obtained. The implications for the actual degree of protection against infection are unknown, since this will depend also on whether the vaccine has elicited an immunological memory response. Individuals with complement deficiencies and individuals with functional or anatomical asplenia may mount an immune response to meningococcal serogroup C conjugate vaccines; however, the degree of protection that would be afforded is unknown.

Immunisation with this vaccine does not substitute for routine diphtheria vaccination.

Meningitec SHOULD UNDER NO CIRCUMSTANCES BE ADMINISTERED INTRAVENOUSLY.

4.5 Interaction with other medicinal products and other forms of interaction

Meningitec must not be mixed with other vaccines in the same syringe. Separate injection sites should be used if more than one vaccine is being administered.

Administration of Meningitec at the same time as (but, for injected vaccines, at a different injection site) the following vaccines did not reduce the immunological response to any of these other antigens in clinical trials:
Oral Polio vaccine (OPV); Inactivated Polio vaccine (IPV); Hepatitis B vaccine (HBV); diphtheria and tetanus vaccine alone (D or T), in combination (DT or dT), or in combination with whole cell or acellular Pertussis vaccine (DTwP or DTaP); *Haemophilus influenzae* type b conjugate vaccine (Hib alone or in combination with other antigens) or combined Measles, Mumps, and Rubella vaccine (MMR).

Minor variations in geometric mean antibody concentrations (GMCs) or titres (GMTs) were observed between studies; however, the clinical significance, if any, of these observations is not established.

Data that support concomitant administration of Meningitec and an acellular Pertussis vaccine (i.e. DTaP) or an Inactivated Polio vaccine (IPV) are derived from studies in which subjects received either Meningitec or the same meningococcal serogroup C conjugate as in Meningitec combined with an investigational pneumococcal conjugate vaccine and from a study of concomitant administration with a pediatric combination vaccine (DTaP-HBV-IPV/Hib).

In various studies with different vaccines, concomitant administration of meningococcal serogroup C conjugates with combinations containing acellular pertussis components (with or without inactivated polio viruses, hepatitis B surface antigen or Hib conjugates) has been shown to result in lower SBA GMTs compared to separate administrations or to co-administration with whole cell pertussis vaccines. The proportions reaching SBA titres of at least 1:8 or 1:128 are not affected. At present, the potential implications of these observations for the duration of protection are not known.

Data on concomitant administration of Meningitec with 7-valent pneumococcal conjugate vaccine (Prevenar) are not available. However, data from an investigational combination vaccine (9-valent pneumococcal-CRM_{197} protein conjugate vaccine and meningococcal serogroup C-CRM_{197} protein conjugate vaccine [9vPnC-MnCC]) containing amongst others the same 7 conjugated pneumococcal serotypes as Prevenar have shown that meningococcal serogroup C (MnC) serum bactericidal antibodies (SBA) titres were lower in recipients of this combination than those receiving Meningitec alone, although almost all subjects achieved a titre of at least 1:8.

One study using a 2, 3 and 4 month schedule showed that 75% and 79% of vaccinees in two groups that received Meningitec alone for the primary series still had SBA titres of at least 1:8 at 12 months of age compared to only 28% and 31% in the two groups primed with the 9vPnC-MnCC vaccine. One month following the twelve-month booster dose, 100% of the MnCC group and 100% of the 9vPnC-MnCC group had SBA titres of at least 1:8.

The potential for immune interference in the antibody response between Prevenar and Meningitec should be taken into consideration before concomitant administration of these vaccines as a 2, 3, and 4 month or another primary series schedule. Consideration should also be given to the age at which the booster dose is administered following priming with concomitant Meningitec and Prevenar.

4.6 Pregnancy and lactation

Pregnancy

There are no clinical data on the use of meningococcal serogroup C conjugate vaccine in pregnant women. Animal studies are insufficient with respect to effects on pregnancy and embryonal/foetal development, parturition and postnatal development (see 5.3. Preclinical safety data). The potential risk for humans is unknown.
Nevertheless, considering the severity of meningococcal serogroup C disease, pregnancy should not preclude vaccination when the risk of exposure is clearly defined.

Lactation

The risk-benefit relationship should also be examined before making the decision as to whether immunise during lactation.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Some of the effects mentioned under section 4.8 (Undesirable effects) such as dizziness and somnolence may affect the ability to drive or operate machinery.

4.8 Undesirable effects

Note: the following descriptions of frequency have been defined as: Very common (≥10%); Common (≥1% and <10%); Uncommon (≥0.1% and <1%); Rare (≥0.01% and <0.1%); Very rare (<0.01%), not known (cannot be estimated from the available data).

Adverse Reactions from Clinical Trials

Adverse reactions reported across all age groups are provided below. Adverse reactions were collected on the day of vaccination and the following three days. The majority of reactions were self-limiting and resolved within the follow-up period.

In all age groups injection site reactions (including redness, swelling and tenderness/pain) were very common. However, these were not usually clinically significant. Redness or swelling of at least 3 cm and tenderness interfering with movement for more than 48 hours was infrequent where studied. Transient injection site tenderness was reported in 70% of adults during clinical trials. Fever of at least 38.0°C was common in infants and toddlers and very common in pre-school children, but did not usually exceed 39.1°C, particularly in older age groups.

In infants and toddlers crying was common after vaccination while drowsiness, impaired sleeping, anorexia, diarrhoea and vomiting were very common. Irritability was very common in infants and in toddlers and common in children aged between 3.5 and 6 years. There was no evidence that these were related to Meningitec rather than concomitant vaccines, particularly DTP.

In trials that evaluated three-dose schedules (2, 3 and 4 months or 2, 4 and 6 months) in infants, rates of adverse events did not increase with successive doses with the exception of fever ≥38°C. However, it should be noted that infants received other scheduled vaccines concomitantly with Meningitec in these studies.

Myalgia was common in adults. Somnolence was commonly reported in children between 3.5 and 6 years of age and in adults. Headache was common in children between 3.5 and 6 years of age and was very common in adults.

Adverse reactions reported across all age groups are provided below.

General Disorders and Administration Site Conditions:

Very common:	Injection site reactions (e.g. redness, swelling, pain/tenderness)
Common:	Fever ≥ 38 °C

Additional reactions reported in infants (first year of life) and toddlers (second year of life) are provided below.

Metabolism and Nutrition disorders:
Very common: Anorexia

Psychiatric Disorders:
Very common: Irritability
Common: Crying

Nervous System Disorders:
Very common: Drowsiness, impaired sleeping

Gastrointestinal Disorders:
Very common: Vomiting, diarrhoea

Additional reactions reported in older age groups including adults (4 to 60 years) included:

Psychiatric Disorders:
Common: Irritability (children between 3.5 and 6 years of age)

Nervous System Disorders:
Very common: Headache (adults)
Common: Somnolence, headache (children between 3.5 and 6 years of age)

Musculoskeletal, Connective Tissue and Bone Disorders:
Common: Myalgia (adults)

Adverse Reactions from Post Marketing Surveillance (for all age groups)

These frequencies are based on spontaneous reporting rates and have been calculated using number of reports and number of doses distributed.

Blood and Lymphatic System Disorders:
Very rare: Lymphadenopathy

Immune System Disorders:
Very rare: Anaphylactoid/anaphylactic reactions including shock, hypersensitivity reactions including bronchospasm, facial oedema and angioedema

Nervous System Disorders:
Very rare: Dizziness, faints, seizures (convulsions) including febrile seizures and seizures in patients with pre-existing seizure disorders, hypoaesthesia, paraesthesia and hypotonia (including hypotonic-hyporesponsive episode [HHE])

There have been very rare reports of seizures following Meningitec vaccination; individuals have usually rapidly recovered. Some of the reported seizures may have been faints. The reporting rate of seizures was below the background rate of epilepsy in children. In infants seizures were usually associated with fever and were likely to be febrile convulsions.

There have been very rare spontaneous reports of hypotonic-hyporesponsive episode (HHE), a condition characterised by hypotonia and reduced responsiveness in association with pallor or cyanosis, in temporal association with the administration of meningococcal serogroup C conjugate vaccine. In most cases, meningococcal serogroup C conjugate vaccine was administered concomitantly with other vaccines, the majority of which were pertussis-containing vaccines.

Gastrointestinal Disorders:
Very rare: Vomiting, nausea, abdominal pain

Skin and Subcutaneous Tissue Disorders:
Very rare: Rash, urticaria, pruritus, erythema multiforme, Stevens-Johnson syndrome

Musculoskeletal, Connective Tissue and Bone Disorders:
Very rare: Arthralgia

Renal and Urinary Disorders:
Relapse of nephrotic syndrome has been reported in association with Meningococcal serogroup C conjugate vaccines.

Very rarely, petechiae and/or purpura have been reported following immunisation (see also section 4.4).

4.9 Overdose

There have been reports of overdose with Meningitec, including cases of administration of a higher than recommended dose at one visit, cases of subsequent doses administered closer than recommended to the previous dose, and cases in which the recommended total number of doses has been exceeded. Most individuals were asymptomatic. In general, adverse events reported with overdosage have also been reported with recommended single doses of Meningitec.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: *Meningococcal vaccines*, ATC code: *J07AH*

Immunogenicity

No prospective efficacy trials have been performed.
Serological correlates for protection have not been definitively established for conjugated meningococcal C vaccines; these are under study.
The serum bactericidal antibody (SBA) assay referenced in the text below, used rabbit serum as a source of complement.

Primary Series in Infants

Two doses in infants provided SBA antibody titres (using baby rabbit complement) ≥1:8 in 98-99.5% of infants, as shown in the Table below. A two-dose infant schedule primed for a memory response to a booster dose given at 12 months of age.

% of subjects achieving ≥1:8 SBA titres (GMT)

STUDY with Meningitec given at age	AFTER 2ND DOSE	AFTER 12-MONTH booster
2, 3, 4 months with concomitant DTwP-Hib and OPV	98% (766) n=55	(Not studied)
3, 5, 7 months given alone	99.5% (1591)# n=214	(Not studied)
2, 4, 6 months with concomitant DTaP-HBV-IPV/Hib*	99.5% (1034)# n=218	(Not studied)
3, 5 months administered as 9vPnC-MnCC with concomitant DTaP-IPV/Hib	98.2% (572) n=56	100% (1928) n=23 (9vPnC-MnCC booster)
		100% (2623) n=28 (Meningitec+23vPnPS booster)

* See section 4.5
# measured at two months after the second dose
MnCC = meningococcal serogroup C conjugate vaccine (which is the active component in Meningitec)
DTwP = whole cell pertussis vaccine with diphtheria and tetanus toxoids
OPV = oral polio virus vaccine
DTaP-IPV/Hib = acellular pertussis components, diphtheria and tetanus toxoids, inactivated polioviruses and a Hib conjugate (tetanus toxoid carrier protein)
DTaP-HBV-IPV/Hib = as above plus recombinant hepatitis B surface antigen in a hexavalent formulation
9v-PnC-MnCC = investigational 9-valent pneumococcal conjugate vaccine (not licensed) formulated with meningococcal serogroup C conjugate vaccine (which is the active component in Meningitec)
23vPnPS = 23-valent pneumococcal polysaccharide vaccine

Immunogenicity of a single primary dose in toddlers

91% of 75 toddlers of 13 months of age developed SBA titers ≥ 1/8 and 89% of these 75 subjects showed a four-fold increase over their pre-vaccination antibody titre after receiving a single dose of Meningitec.

Immunogenicity of a single primary dose in adults

All the 15 adults of 18-60 years who received a single dose of Meningitec achieved SBA titers ≥ 1/8 and a four-fold rise in antibody titre.
There are no data in adults aged 65 years and older.

Post-marketing surveillance following an immunisation campaign in the UK

Estimates of vaccine effectiveness from the UK's routine immunisation programme (using various quantities of three meningococcal serogroup 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% CI: 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.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Female mice were immunised intramuscularly with twice the clinical dose of meningococcal serogroup C conjugate vaccine, either prior to mating or during the gestation period. Gross necropsy of viscera was performed on each mouse. All mice survived to either delivery or caesarean-section. No adverse clinical signs were present in any mouse and no parameters that were evaluated were affected by administration of the vaccine, in either the adult or foetal mice.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

18 months.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Discard if the vaccine has been frozen.
Store in the original package.

6.5 Nature and contents of container

0.5 ml of suspension in a pre-filled syringe (type I glass) and a plunger stopper (gray butyl rubber). Pack sizes of 1 and 10 pre-filled syringes with or without needle.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Upon storage, a white deposit and clear supernatant can be observed.

The vaccine should be well shaken in order to obtain a homogeneous white suspension and visually inspected for any foreign particulate matter and/or variation of physical aspect prior to administration. If this is observed, discard the vaccine.

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

7 MARKETING AUTHORISATION HOLDER

John Wyeth & Brother Limited
Huntercombe Lane South
Taplow, Maidenhead
Berkshire SL6 0PH
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00011/0496

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/09/2007

10 DATE OF REVISION OF THE TEXT

19/09/2007

Module 3
Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

P422865

Meningitec suspension for injection in pre-filled syringe
Meningococcal serogroup C oligosaccharide conjugate vaccine (adsorbed)

[redacted]

Meningitec suspension for injection in pre-filled syringe
Meningococcal serogroup C oligosaccharide conjugate vaccine (adsorbed)

P422865

Read all of this leaflet carefully before you/your child receives 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 you/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.

Medicinal product subject to medical prescription.

In this leaflet:

1. WHAT MENINGITEC IS AND WHAT IT IS USED FOR

Meningitec is a meningococcal serogroup C vaccine.

Meningitec helps protect your child against diseases such as : meningitis and septicaemia (blood poisoning).

Meningitec is a vaccine that is used in children from 2 months of age, adolescents and adults to help prevent infections caused by bacteria called *Neisseria meningitidis* serogroup C. It will not protect against other serogroups of *Neisseria meningitidis* or other bacteria or viruses that sometimes cause meningitis and septicaemia (blood poisoning). The vaccine works by causing your body to produce its own protection (antibodies) against this bacteria. *Neisseria meningitidis* serogroup C bacteria can cause serious and sometimes life-threatening infections such as meningitis and septicaemia (blood poisoning).
This vaccine contains no live organism and it cannot cause meningitis C (meningococcal C disease).

Remember that no vaccine can provide complete and life-long protection in all people vaccinated.

2. BEFORE YOU/YOUR CHILD RECEIVE MENINGITEC

Do not use Meningitec
- if you/your child are allergic (hypersensitive) to the active substances or any of the other ingredients of Meningitec.
- if you/your child have shown signs of an allergic reaction to any other vaccine that contains diphtheria toxoid or the diphtheria CRM_{197} protein.
- if you/your child have shown signs of an allergic reaction to a previous dose of Meningitec.
- if you/your child have an illness with a high temperature, vaccination is usually postponed but it can go ahead if the fever and illness are only mild, but talk to your doctor or nurse first.

Take special care with Meningitec
- if you/your child have haemophilia or any other problem that may stop your blood from clotting properly, or if you/your child are taking any medicines that stop your blood from clotting properly. If so, your doctor may choose to take special precautions.
- if you/your child have a weak immune system, or if you/your child have recently had or are currently having a course of treatment with radiation, corticosteroids or any other medicines that can lower your immunity to infections. Meningitec can still be given but it may not protect as well as in other people.
- if you/your child suffer from a kidney disease in which large amounts of protein appear in the urine (called nephrotic syndrome). There have been reports of relapse of this condition after vaccination. Your doctor will advise you if you can still have Meningitec depending on the exact type of kidney problem you have.

Although Meningitec contains a protein (called CRM_{197}) from the bacteria that cause diphtheria, it does not protect against diphtheria disease, so it is important that you/your child receives other vaccines that protect against diphtheria when these are due. Your doctor or nurse can advise you.

Meningitec has been given mainly to infants from the age of 2 months, children and young adults. No information is yet available about giving Meningitec to people aged 65 years and over or infants under the age of 2 months.

Using other medicines

Please tell your doctor or pharmacist if you/your child are taking or have recently taken any other medicines, including medicines obtained without a prescription or has recently received any other vaccines.
Unless told otherwise by your doctor or nurse, you/your child should continue to take prescribed medicines as usual before and after vaccination.

Meningitec can be given at the same time as other vaccines against one or more of following diseases:
Polio (including vaccines against polio that are given by mouth or by injections)
Diphtheria
Tetanus
Whooping cough (pertussis)
Haemophilus influenzae type b (known as Hib vaccines)
Hepatitis B
Measles, mumps and rubella (German measles)
Meningitec may also be given at the same time as pneumococcal 7-valent vaccine, which is a vaccine against pneumococcal infection.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine, including vaccinations. Meningitec would not usually be given to pregnant or breast feeding women unless it is thought very necessary by your doctor that the pregnant or breast feeding women should be vaccinated as soon as possible.

Driving and using machines
After receiving Meningitec, sleepiness, dizziness and other side effects may occur that could interfere with driving or operating machinery (see possible side effects).

Do not drive or operate machinery until you know how Meningitec affects you.

Important information about some of the ingredients of Meningitec
One of the ingredients of Meningitec is sodium chloride. This vaccine contains less than 1 mmol of sodium (23 mg) per 0.5 ml dose and is therefore essentially 'sodium free'.

3. HOW MENINGITEC IS GIVEN

Meningitec will be given to you/your child by a doctor or nurse.

Your doctor or nurse will make sure that the vaccine is injected correctly into a muscle (not into or near nerves or blood vessels or too shallow under the skin) and that Meningitec is not mixed with other vaccines in the same syringe. The vaccine is a 0.5 ml injection and it is usually given into the muscle of the thigh in infants and into the shoulder muscle for older children, adolescents and adults. It should not be given into the buttock area.

For infants 2 months up to 12 months of age, two doses of Meningitec should be given at least two months apart.

In order to maintain protection, a booster dose should be given after the infant course of two doses has been completed. Your doctor will advise you when your child should receive this.

For adults, adolescents and children over the age of 12 months who have not previously been immunised with Meningitec, a single dose (0.5 ml) of the vaccine is recommended.

Meningitec will be given as a separate injection into a different body site when it is given at the same time as another injected vaccine.

If you use more Meningitec than you should
Overdose is very unlikely because the vaccine is provided in single-dose pre-filled syringes and is given by a doctor or nurse.

There have been a few reports of too many doses being given, too much vaccine being given, or doses being given too close together. In most cases, there were no side effects while sometimes there were side effects that were similar to those seen after routine and correct use of Meningitec.

If you forget to go to the doctor
If you forgot to go to the doctor or nurse at the scheduled time, ask your doctor or nurse for advice.

4. POSSIBLE SIDE EFFECTS

Like all vaccines, Meningitec can cause side effects, although not everybody gets them.

Serious allergic reactions are always a very rare possibility after receiving a vaccine. These reactions may include :

- swollen face, tongue of pharynx,
- difficulty to swallow
- skin swelling (hives) and difficulties to breathe,
- low blood pressure causing collapse and shock.

When these signs or symptoms occur they usually develop very quickly after the injection is given and while the person affected is still in the clinic or doctor's surgery. If any of these symptoms occur after leaving the place where your injection was given, you must consult a doctor IMMEDIATELY.

Very rarely, severe skin rashes can occur that can cover much of the body and lead to blistering and peeling. The inside of the mouth and the eyes can also be affected. Other less serious allergic reactions include rashes that may be red and lumpy, itching, and a later general illness that can cause symptoms such as fever and swelling of the joints.

This vaccine cannot cause meningitis C (meningococcal C disease). If you or 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 you/your child suffer 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 after vaccination.

The frequencies of side effects that are described in this section are:
Very common = occurred in more than one in ten people who received the vaccine.
Common = occurred in between one in ten and one in a hundred people who received the vaccine.
Very Rare = occurred in less than one in ten thousand people who received the vaccine.

Very Common side effects include:
In all age groups - swelling and tenderness or pain at the injection site.
In infants and toddlers - loss of appetite, irritability, sleepiness or disturbances of sleeping patterns, being sick, diarrhoea.
In adults – headaches.
In pre-school children – fever.

Common side effects include:
In all age groups - fever (very common in pre-school children), but this is rarely severe.
In infants and toddlers – crying.
In children between 3-6 years – sleepiness, headache, irritability.
In adults – muscle pains, sleepiness.

Very rare side effects include (in all age groups unless already mentioned above):
Swelling of the glands, dizziness, faints, numbness, tingling sensation or pins and needles, feeling or being sick, bruising or bleeding into the skin, relapses of certain kidney disorders in which large amounts of protein appear in the urine.
Very rarely a reduction in muscle tone has been observed (floppiness), sometimes with reduced alertness or responsiveness of the infant and a pale or bluish appearance to the skin.
Fits (seizures) have been reported very rarely after vaccination with Meningitec including some fits in people who already had fits at times. In teenagers and adults, some of the reports of fits may actually

have been fainting attacks. In infants and young children seizures were usually associated with fever and were likely to be febrile convulsions. Most people recovered rapidly after the fit.

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 MENINGITEC

Keep out of the reach and sight of children.

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

Store in a refrigerator (+2°C to +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 Meningitec contains

The active substances
Each 0.5 ml dose contains:
Meningococcal serogroup C oligosaccharide*
10 micrograms
*conjugated to the CRM_{197} carrier protein and adsorbed on aluminium phosphate (0.125 mg)

The other ingredients are sodium chloride and water for injections.

What Meningitec looks like and contents of the pack

Meningitec is a suspension for injection supplied in pre-filled syringes of 0.5 ml in pack sizes of 1 and 10 (with or without needle). **After shaking, the vaccine is a homogeneous, white suspension.** Not all pack sizes may be marketed.

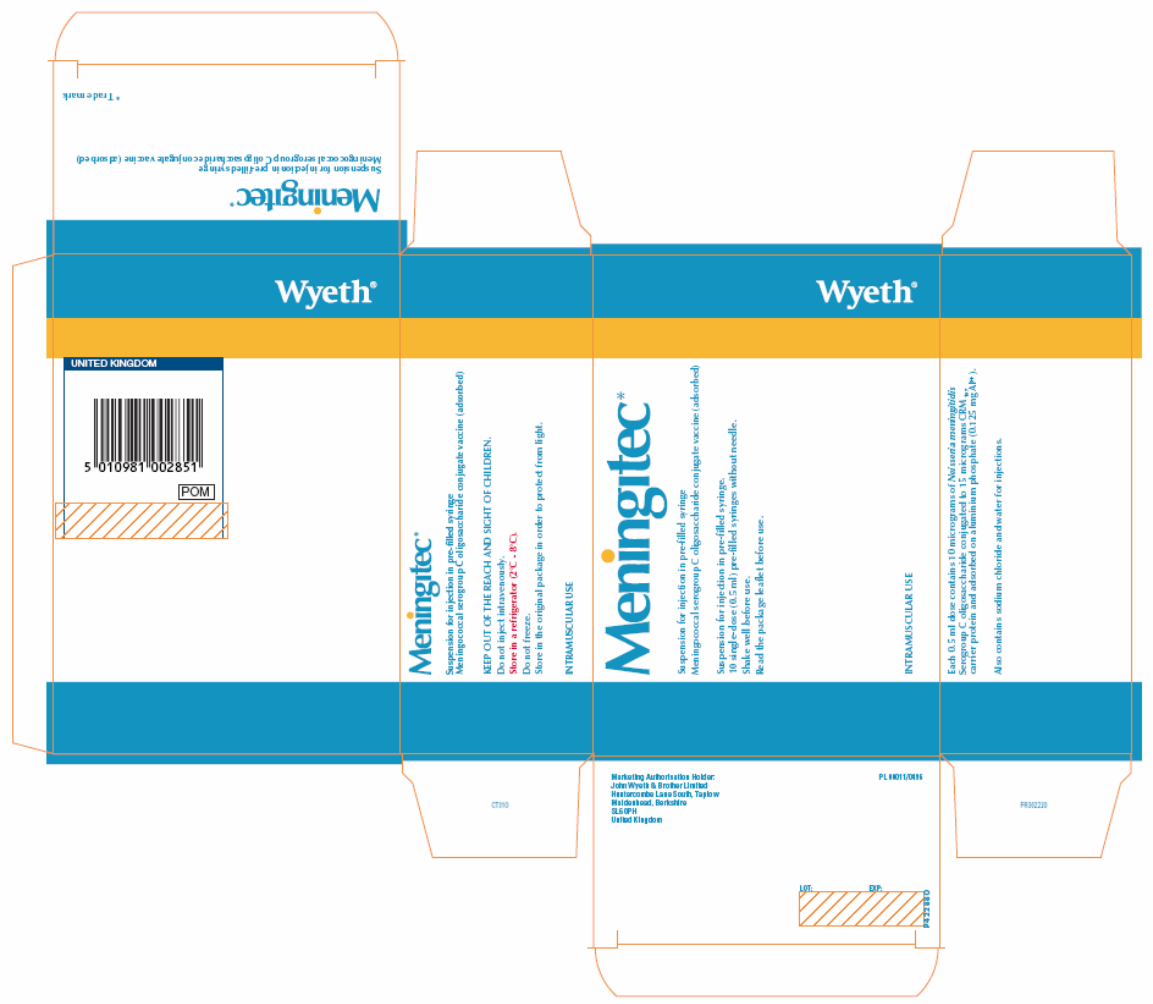
Marketing Authorisation Holder and Manufacturer

- Marketing Authorisation Holder
  John Wyeth & Brother Limited
  Huntercombe Lane South
  Taplow, Maidenhead
  Berkshire SL6 0PH
  United Kingdom
- Manufacturer responsible for batch release
  Wyeth Pharmaceuticals
  New Lane
  Havant P09 2NG
  United Kingdom

This leaflet was last approved in August 2007

PR302220

Module 4
Labelling


Wyeth®
UNITED KINGDOM
5 010981 002851
POM
Meningitec®
Suspension for injection in pre-filled syringe
Meningococcal serogroup C oligosaccharide conjugate vaccine (adsorbed)
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Do not inject intravenously.
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Store in the original package in order to protect from light.
INTRAMUSCULAR USE
CT390
Wyeth®
Meningitec®
Suspension for injection in pre-filled syringe
Meningococcal serogroup C oligosaccharide conjugate vaccine (adsorbed)
Suspension for injection in pre-filled syringe.
10 single-dose (0.5 ml) pre-filled syringes without needle.
Shake well before use.
Read the package leaflet before use.
INTRAMUSCULAR USE
Each 0.5 ml dose contains 10 micrograms of *Neisseria meningitidis*
Serogroup C oligosaccharide conjugated to 15 micrograms CRM197
carrier protein and adsorbed on aluminium phosphate (0.125 mg Al3+).
Also contains sodium chloride and water for injections.
Marketing Authorisation Holder:
John Wyeth & Brother Limited
Huntercombe Lane South, Taplow
Maidenhead, Berkshire
SL6 0PH
United Kingdom
PL 11011/0016
LOT:
EXP:
P8302230

Module 5

Scientific discussion during initial procedure

1. INTRODUCTION

Background

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Meningitec was approvable. Meningitec is indicated for use in the active immunisation of children from 2 months of age, adolescents and adults for the prevention of invasive disease caused by *Neisseria meningitidis* serogroup C. The use of Meningitec should be determined on the basis of official recommendations.

Meningitec suspension for injection in vials (PL 00011/0245) was granted a marketing authorisation in the UK on 15th October 1999.

Meningitec is approved via the mutual recognition procedure in the European Union with a single dose (0.5mL) glass vial as container. The Marketing Authorisation Holder, John Wyeth & Brother Ltd applied for marketing authorisations in several CMS's via two mutual recognition procedures as outlined below.

A first use mutual recognition procedure determined on 17th August 2000 led to the grant of marketing authorisation in: Belgium, Germany, Greece, Ireland, Luxembourg, Portugal, Spain.

A repeat use (2nd wave) mutual recognition procedure determined on 28th August 2002 led to the grant of marketing authorisation in: Austria, Denmark, Finland, France, Iceland, Italy, The Netherlands, Norway, Sweden.

National Marketing Authorisations also exist in Cyprus, Malta, Hungary, Poland and Switzerland.

In order to introduce a new container of Meningitec (PL 00011/0496), the single dose pre-filled glass syringe also containing 0.5ml, the Marketing Authorisation Holder applied for marketing authorisations of the new product in several CMS's via one decentralised procedure as outlined below. The pre-filled syringe presentation was not currently licensed in any other Member State.

A decentralised procedure determined on 24th September 2007 led to the grant of marketing authorisation in: Austria, Belgium, Germany, Denmark, Greece, Spain, Finland, France, Ireland, Iceland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Sweden.

Overall Benefit/Risk Assessment

The RMS has been assured that acceptable standards of 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.
The RMS has been assured that acceptable standards of GMP are in place for these product types at

all sites responsible for the manufacture and assembly of this product. 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.

Non-clinical studies were carried out in accordance with Good Laboratory Practice (GLP), and in accordance with recognised guidelines. No unexpected toxicity was demonstrated, and no new toxicological problems for the product were observed.

The clinical efficacy and safety of this product is the same as that of Meningitec presented in vials. Clinical studies on Meningitec were carried out in accordance with Good Clinical Practice (GCP).

2. PHARMACEUTICAL ASSESSMENT

REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION

N/A

INTRODUCTION

This application has been made to register the product Meningitec® in a pre-filled syringe presentation. Meningitec® suspension for injection in vials (UK/H/0356/01)is currently registered in Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, and UK, under the Mutual Recognition Procedure for which the UK is RMS.

National Marketing Authorisations exist in Cyprus, Malta, Hungary, Poland and Switzerland.

The current submission is an Extension to UK/H/0356/01 as outlined in Annex II of EC 1084/2003 for a new pharmaceutical form. In the case of the submitted application, the change from a vial to a pre-filled syringe formulation is defined as a new pharmaceutical form as described in NtA "Guideline on the categorisation of extension applications versus variations applications". The application is submitted in accordance with Directive 2001/83/EC as amended under the Decentralised Procedure. The Reference Member State is to be the UK and Concerned Member States are: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain and Sweden.

DRUG SUBSTANCE

I.1 General Information

I.2 Manufacture

The manufacture of the active substance occurs at the below two sites:

Manufacturing site for CRM_{197} and MnC polysaccharide
Sanford: Wyeth Pharmaceuticals, Division of Wyeth Holdings Corporation
4300 Oak Park
Sanford, NC 27330
United States

Manufacturing site for MnC oligosaccharide and MnC conjugate
Berna Biotech AG (Berna Biotech Limited)
Rehhagstrasse 79
CH-3018, Berne
Switzerland

A declaration that manufacture is conducted to EU GMP standards is provided.

I.3 Evaluation of drug substance

In line with the requirements of a line extension, the applicant has provided a complete module 3, including those sections relating to the active substance. All sections are principally the same as those for UK/H/0356/01 (Meningitec presented in vials). All differences between the proposed section 3.2.S and that of UK/H/0356/01 have been provided.

The differences relate to aligning the dossier with approved variations, correcting typographical errors, clarifying the text, updates in line PhEur and inclusion of additional batch and stability data.

Drug Product

I.4 Description and Composition of the Drug Product

Each 0.5 mL dose contains
Meningococcal group C Oligosaccharide-CRM197-conjugate (MnCC) 10 µg saccharide 15 µg CRM197

Name of Ingredients	Function	Reference standard
Active Substance Meningococcal group C Oligosaccharide-CRM197-conjugate (MnCC)	Antigen	Internal Monograph
Excipients Sodium chloride Water for Injections	 Excipient Solvent	 PhEur PhEur
Adjuvant Aluminium phosphate	 Adjuvant	 Internal Monograph

Table 1: Composition of Meningitec

I.5 Pharmaceutical Development

The pharmaceutical development of the pre-filled syringe presentation of Meningitec is based on data from the vial presentation and is identical to that registered for the vials.

Three pilot scale and three validation batches of Meningitec pre-filled syringes have been manufactured using three different batches of formulated bulk produced for filling of Meningitec in vials.

The formulation process and all specifications will remain the same. A comparison between both locations is listed in section 3.2.P.3.5.

The objective of this application is the presentation of the finished product. The proposed license is to utilise a sterile depyrogenated ml syringe composed of low alkalinity type I glass and a grey-butyl rubber plunger stopper. The vial presentation is a sterile depyrogenated 3ml capacity vial composed of type I glass and a 13mm grey-butyl rubber stopper.

Full details of the proposed presentation and how it compares to the vial were provided.

The integrity of the container closure system has been investigated using the dynamic dye challenge and the static microbial challenge.

Manufacture

Manufacturers

Berna Biotech Ltd
Rehhagstrasse 79
3018, Berne
Switzerland*Function*
Manufacture of final formulated bulk

Aluminium Phosphate Adjuvant
Wyeth Pharmaceuticals Division of Wyeth Holdings Corporation
401 North Middletown Road
Pearl River
NY 10965
USA

Function
Manufacture of the aluminium phosphate adjuvant

Berna Biotech Espana, S.A.
Ctr. N-I, KM 20, 900
28700 San Sebastian de los Reyes
Madrid
Spain

Function
Manufacturing site for final filled syringe filling
Labelling and packaging

Wyeth Pharmaceuticals
New Lane
Havant
PO29 2NG

Function
Labelling and packaging
Batch Release

Description of Manufacturing Process and Process Controls

The active ingredient of the *Neisseria meningitidis* group C conjugate vaccine, Meningitec is MnCC.

Formulation of the finished product is divided into two parts:

- MnCC to 80% formulated bulk

This involves the dilution of MnC conjugate with 0.85% sodium chloride (NaCl) solution to achieve a 25µg/ml concentration of saccharide required for vaccine manufacture.

- 80% formulated bulk to MnCC formulated bulk

The main operation during this stage of the process is the adsorption of the formulated bulk onto aluminium phosphate adjuvant and the dilution to the final desired level of saccharide concentration for vaccine manufacture.

The MnCC formulated bulk is stored at 2-8°C.

The storage times for each of the intermediates were provided

In-process controls

Tests	Methods	Limit
Saccharide content (PV8177)	NANA assay	20-30 µg

In-process controls for MnCC bulk

Filling Process

A validated shipping procedure is used to ship Meningitec formulated bulk from Berna Biotech Ltd (Switzerland) to Berna Biotech España, (Spain).
Upon receipt by the Berna Biotech España warehouse, MnCC formulated bulk is stored at 2-8°C prior to filling.
During the filling process, formulated bulk is filled into sterile syringe barrels (target of 0.57 mL) that are subsequently closed with sterile plunger stoppers. In case of an interruption of the filling process for more than 3 mins, the filling machine changes to recirculation mode via a recirculation valve into the surge vessel.

Sterilised, siliconised plunger stoppers are used to seal the syringes.

- Syringes are 100% inspected for cosmetic and particulate defects.

Following inspection, the syringes are packaged and shipped to the UK

The in-process controls of the filling area are:
Turbidity
Fill weight checks
Headspace
Visual inspection

Process Validation

Three pilot scale and three validation batches of Meningitec filled syringe have been manufactured using portions of three different formulated bulks produced for filling of Meningitec in vials. The three formulated bulk batches were manufactured at Berna Biotech Ltd The applicant have moved all formulation activities performed in building 74 at Berna Biotech Ltd (Grafenried site) to building 81j at Berna Biotech Ltd (Rehhag site).

The process validation lots will be enrolled in a stability program at 2-8°C.

The filling of the syringes has been validated using media fill studies.

Testing performed included; filling weight, turbidity, saccharide content, endotoxin, pH, appearance, MnC saccharide identity CRM197 identity and sterility. All tests were within specification.

The filling batch size of Meningitec filled Syringes is approximately 40,000 to 150,000 syringes. The filling process is normally completed within 2 days including preparation of the 100L tank and filling equipment setup.

I.6 Excipients

The excipients used in the manufacturing process are sodium chloride, water for injections and aluminium phosphate. Sodium chloride and water for injections are both controlled to PhEur specifications.

Aluminium phosphate is controlled to an in-house specification and manufactured at Wyeth Pharmaceuticals Division of Wyeth Holdings Corporation in Pearl River, New York, USA.

No changes to this section have been made compared with the vial presentation of Meningitec.

I.7 Control of Drug Product

The following control tests are conducted on the formulated bulk and are considered adequate:

Appearance
PH
Identity
- CRM_{197}
- MnC saccharide

Saccharide content
Aluminium content
Endotoxin Content
Sterility

The following control tests for the formulated bulk are conducted and are considered adequate:

Appearance
pH
Identity
- CRM_{197}
- MnC saccharide

Saccharide content
Aluminium content
Free saccharide
Extractable volume
Endotoxin Content
Sterility

The specifications of the formulated bulk have been modified compared with the vial presentation to include an additional test for antigen adsorption and by changing the analytical method for aluminium content from atomic absorption to inductively coupled plasma/optical emission spectroscopy.

The specification of the final filled syringe has been modified to include a test for extractable volume. All other tests and limits are identical those in the vial dossier.

Analytical procedures

The analytical procedures and their validation for both the bulk product and filled syringes are the same as those used for the vial presentation. The exception to this is the additional test for antigen adsorption and the use of inductively coupled plasma/optical emission spectroscopy to quantify aluminium content in the bulk product. With respect to the filled syringe, an additional test method for extractable volume has been included.

Batch Analysis

Batch analyses from three batches of the formulated bulk have been provided.
All specifications were met.

Justification of specifications

The tests selected for routine use in the control and release of the Meningitec filled syringe vaccine are based in part on the tests recommended by the PhEur monograph on Meningococcal Group C Conjugate Vaccine and on injectable products (extractable volume), and in part on the registered MnCC vial vaccine.

I.8 Container Closure System

The container closure system proposed for this product is a 1ml pre-sterilised type I glass syringe with a Luerlok® adaptor (non product contact) closed on one side by a rubber tip cap and on the other side by a grey butyl rubber plunger stopper. A polypropylene plunger rod is then inserted into the rubber plunger stopper and a backstop (polypropylene) is put on the syringe flange, after which

the entire assembly is packed in a preformed tray and inserted into a cardboard box. The box contains the patient information leaflet and may also contain a sterilised needle.

The syringe barrel consists of a pre-sterilised barrel of PhEur type I borosilicate glass. The tip cap consists of grey butyl rubber formula 7025. The Luerlok® adaptor consists of clear polycarbonate.

A sterile needle may be included in the pack (see under medical devices).

I.9 Stability

Stability data provided for the bulk vaccine support the shelf life of 6 months at 2-8ºC

Results from the stability studies support the 18 months shelf life.

REGIONAL INFORMATION

Medical Device issues

A sterile K-pack II Needle (25Gx5/8" or 25Gx1") is to be included in the outer carton with the 1x1 single-dose glass pre-filled syringe pack size. K-pack II Needle is a sterile hypodermic needle manufactured by Terumo Europe N.V. and is in compliance with the European Medical Devices Regulations and is CE marked.

TSE Issues
A TSE certificate for charcoal is included as detailed in section V.
The other materials of animal origin used in the process are bovine milk derivatives from the USA, Australia and New Zealand and an enzymatic system from a porcine (pancreas) source. This material is in compliance with the guidance given to minimise the risk from TSE infections

PHARMACEUTICAL ASSESSMENT of THE SPC, LABELS AND PACKAGE LEAFLET

The SPC for Meningitec pre-filled syringes is based on the SPC for the vial presentation. The proposed SPC has been updated in line with the QRD template and the SPC Guideline dated October 2005 and to reflect the changes from vial to pre-filled syringe

The label and leaflet are in line with the QRD templates.

Consultation with patient groups has been performed by the applicant. Two set of 10 patients from a range of demographics were used. A total of 15 questions were asked. The questions and subjects selected were appropriate.

ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY

The application for a line extension to Meningitec® suspension for injection is approvable.

3. NON CLINICAL ASSESSMENT

I. INTRODUCTION

Meningitec suspension for injection in vials is currently registered in the UK and all Concerned Member States and it was considered acceptable that the applicant refer to the non-clinical documentation for the currently approved product in support of this product and therefore no new non-clinical data were submitted.

II. ENVIRONMENTAL RISK ASSESSMENT

The pre-filled syringe will replace the vial presentation and so this change will not increase the environmental exposure of the product. Therefore an Environmental Assessment Report is not provided with the application.

III. ASSESSOR'S OVERALL CONCLUSIONS

Potential issues that need to be considered relate to the compatibility of the suspension with the materials in the syringe and effects on the environment. On each aspect, no concerns are raised, and no objections to the grant of an approval on preclinical grounds, were raised.

4. CLINICAL ASSESSMENT

I. INTRODUCTION

Since the final assessment report was written, several variations have been approved. Variation assessment reports were therefore attached as appendices.

Neisseria meningitidis infection is a major cause of septicaemia and meningitis at all ages, and in fulminant cases proves rapidly fatal. With the dramatic reduction in invasive *Haemophilus influenzae* type b infections following the introduction of infant immunisation with conjugate vaccines, meningococcal infection is now the commonest cause of meningitis in the United Kingdom.

In England and Wales, most episodes of meningococcal disease are caused by *Neisseria meningitidis* serogroup B. However, the percentage caused by serogroup C has increased in latter years. From 1996-1998 more deaths were associated with serogroup C (approximately 50-150 a year) than with serogroup B, with peaks in the death rate in the age groups 1-4 and 15-19. Epidemiological data for other Member States included in this Mutual Recognition Procedure are included in the Clinical Expert Report.

The clinical efficacy section of this application is based on demonstration of adequate immunogenicity.
Efficacy studies have not been performed, the justification being:

- meningococcal polysaccharide vaccines are already licensed, and levels of serum bactericidal activity associated with protection against invasive disease have been determined.
- the size of efficacy trial that would be required is so great as to be impracticable (an informal estimate puts this at the entire UK child population followed for two or more years).
- experience with the very similar *Haemophilus influenzae* conjugate vaccine suggests that adequate levels of immunogenicity are associated with high levels of protection and dramatic reductions in disease incidence

I.2 Regulatory status

- This was the ***first application*** for a conjugate meningococcal serogroup C vaccine in any country (EU and non-EU).

- ***The UK licence*** was granted on October 15th 1999, and this was recognised (after SPC modification) by ***seven other EU MS*** on July 11th, 2000.

- ***During the first MRP***, the UK's Committee on Safety of Medicines (CSM) reviewed the adverse event profile of this vaccine and recommended modifications of section 4.8; these were incorporated into the SPC during the MRP.

- ***Subsequently, and before initiation of this second MRP***, the applicant submitted a Type II variation to further update section 4.8 based on the results of the first PSUR. The Assessment Report on these data is appended.

- ***The final SPC*** after all the above procedures is appended to the variation assessment report on pages 12-16, along with ***the final UK PIL*** (pages 17-19)**.**

- The applicant's ***Clinical Expert Report*** has been updated to incorporate all the above information and is appended to this report on pages 37-75.

I.3 Indications

Active immunisation of children from 2 months of age, adolescents and adults for the prevention of invasive disease caused by Neisseria meningitidis serogroup C

I.4 Dosage and Dosage Schedules

Infants under the age of 12 months: three doses, each of 0.5 mL, the first dose given not earlier than age 2 months and with an interval of at least 1 month between doses. Children over the age of 12 months, adolescents and adults: a single dose of 0.5 mL

I.5 Overview of Clinical Trials

Data from 11 studies, 7 in infants (aged less than one year) and 4 in older patients, were included in the original dossier (see next page).

During the first MRP, into seven countries, the company provided additional data from two of the trials on this list (D110P802 and D118P8). These data have been incorporated into this assessment report.

The applicant also provided a list of pertinent ongoing trials, the results of which may ultimately need to be reflected in the SPC and/or may strengthen the statements made thus far regarding co-administration of Meningitec with other vaccines. Although results from these three trials will not be available until at least June 2001, they may provide additional information on co-administration with IPV and aP-containing products. Meanwhile, it should be noted that almost all UK infants have received Meningitec with a DTaP vaccine from January to November 2000.

Study	Country	Age at entry	No. of Meningitec subjects:	
			Immuno-genicity	Safety
Pilot				
D110P3	USA (Harleysville)	18-44 y	15	15
Dose Determination				
D110P2	UK (PHLS)	8-26 w	47 (2 µg) 48 (10 µg)	115
D124P3	USA (Nashville)	2 m	40 (2 µg) 50 (10 µg)	0
Controlled: infants				
D110P500	UK (Oxford)	2 m	116	122
D118P3	USA (Pittsburgh, Baltimore, Nashville, Atlanta)	2 m	96 Primary 61 Booster	106 Primary 63 Booster
D118P7	USA (Oakland)	2 m	82 Primary 49 Booster	91 Primary 60 Booster
D110P501				
D110P502				
Uncontrolled: infants				
D118P8	USA (Oakland)	2 m	0	2,877
D118P11	USA (Chapel Hill, Durham)	2-11 m	101	0
Uncontrolled: one year olds				
D110P802	UK (Gloucester)	12-17 m	69	73
Controlled: school entry				
D110P801	UK (Gloucester)	3-6 y	0	77
Controlled: students				
D110P805	UK (Southampton, Salford)	18-25 y	112	120

II. PHARMACODYNAMICS

II.1 Definition of immunogenicity

Serum bactericidal assays (SBA) measure functional activity against bacteria. Epidemiological studies have correlated the interval between loss of maternally derived activity and subsequent acquisition of antibody during natural exposure to capsular antigens with known periods of susceptibility to invasive meningococcal disease.
However, a more convenient IgG specific enzyme-linked immuno-absorbent assay (ELISA) has been developed to quantify antibodies to the serogroup C polysaccharide capsule.

In this application, the assays used in individual trials varied in methodologies according to site. The applicant's own laboratories essentially used the CDC-recommended protocols, while those performed at the UK reference laboratory in Manchester used methodologies which varied over time.
Details of these, and a detailed discussion of the implications, are given in the Clinical Expert Report and will not be repeated here. However, it is important to note that these issues make it unreasonable to directly compare results between certain trials.

Using data for SBA and ELISA as performed in Wyeth Lederle Vaccines own laboratories on sera from subsets of infants in two trials, results for the two methods can be correlated as described below.

Study D118-P3 Schedule 2, 4, 6 and (booster) 12-15 months

	ELISA Geometric Mean Concentration (μg/mL IgG to meningococcal C antigen) (95% CI)		**Serum bactericidal assay for Group C meningococcus Geometric Mean Titre** (95% CI)	
Vaccine:	**Meningitec**	**Control**	**Meningitec**	**Control**
n:	30 (49 for booster)	15	30 (49 for booster)	15
Pre	**0.10** (0.06, 0.16)	**0.08** (0.04, 0.17)	**3.6** (1.8, 7.0)	**1.1** (0.9, 1.4)
Post Dose 3	**4.00** (3.26, 5.15)	**0.08** (0.05, 0.11)	**462.6** (315.3, 679.7)	**1.1** (0.9, 1.3)
Pre booster	**0.54** (0.43, 0.67)	**0.15** (0.08, 0.28)	**26.4** (15.7, 44.3)	**3.3** (1.1, 9.5)
Post booster	**7.25** (5.80, 9.07)	**0.12** (0.07, 0.22)	**2341.4** (1588.5, 3451.1)	**3.1** (1.2, 8.3)

Study D110-P500 Schedule 2, 3, 4 months

	ELISA Geometric Mean Concentration (μg/mL IgG to meningococcal C antigen) (95% CI)		Serum bactericidal assay for Group C meningococcus Geometric Mean Titre (95% CI)	
Vaccine:	Meningitec	Control	Meningitec	Control
n:	56	59	56	59
Pre	**0.1** (0.09, 0.17)	**0.2** (0.10, 0.24)	**2.2** (1.5, 3.1)	**2.4** (1.7, 3.5)
Post Dose 3	**24.5** (20.8, 28.9)	**0.1** (0.07, 0.14)	**1428.7** (1130.9, 1805.1)	**2.9** (1.8, 4.8)

Excluding the pre-immunisation results, which reflect a variable amount of maternally derived antibody, pooling of these results for Meningitec showed that when the ELISA IgG concentration is > 1 μg/mL, 98% (lower limit of 95% CI = 95%) of infants have serum bactericidal activity at both 1:4 and 1:8 dilution.
A linear regression model based on log serum bactericidal activity and log IgG showed a strong correlation ($p < 0.001$).
From this model when the ELISA IgG value is ≥ 1.2 μg/mL, the 95% lower confidence limit serum bactericidal titre is ≥ 4, and when the ELISA IgG value is ≥ 2.05 μg/mL, the 95% lower confidence limit serum bactericidal titre is ≥ 8.

II.2 Preliminary trials of immunogenicity and safety

II.2.1 Study No D110 P3 Pilot trial in healthy adults

This randomised, double blind trial compared a single injection of Meningitec with a licensed meningococcal polysaccharide vaccine in healthy adults.
Thirty subjects (18-48 years) were randomised to receive either Meningitec **10 μg** (Batch K2-4-F-05) or unconjugated A, C, Y, W-135 polysaccharide vaccine **50 μg**. ELISA and serum bactericidal activity assays were performed at Wyeth Lederle Laboratories.

IgG GMTs before immunisation and on Day 30 were:

	Meningitec	**Unconjugated polysaccharide**
	n = 15	**n = 15**
Pre		
GMC	**0.4**	**2.2**
95% CI	0.2, 0.8	0.9, 5.2
Post		
GMC	**70.4**	**28.5**
95% CI	39.3, 126.1	11.6, 69.7

Percentages of subjects with antibody levels at specified levels were:

	Meningitec	**Unconjugated polysaccharide**
	n = 15	**n = 15**
Pre		
≥ 1 μg/mL	**27%**	**80%**
≥ 2 μg/mL	**0%**	**47%**
≥ 4 μg/mL	**0%**	**33%**
Post		
≥ 1 μg/mL	**100%**	**100%**
≥ 2 μg/mL	**100%**	**100%**
≥ 4 μg/mL	**100%**	**87%**

Serum bactericidal activity (C11 strain) GMTs (expressed as reciprocal of final dilution yielding ≥ 50% killing) and % subjects achieving titres ≥ 1:8 were:

	Meningitec	**Unconjugated polysaccharide**
	n = 15	**n = 15**
Pre		
GMT	**20**	**70**
Median	8	40
% ≥ 1:8	**100%**	**100%**
Post		
GMT	**7101**	**3579**
Median	8192	8192
% ≥ 1:8	**100%**	**100%**

The conjugate vaccine appeared to stimulate a greater increase in meningococcal Group C antibody, as measured by both IgG concentration and bactericidal titre, for a lesser quantity of antigen.

II.2.2 Study D110 P2 Dose Determination

This unrandomised study assessed the safety and immunogenicity of two different doses of Meningitec, **2μg** (lot number K2-5A-07) and **10μg** (lot number K2-5A-07), given together with routine primary immunisation to UK infants. The first 50 infants were assigned the lower dose and the next 50 the higher dose; 15 were then assigned doses on an alternating basis. ELISA and serum bactericidal activity assays were performed at the Manchester Public Health Laboratory (National Meningococcal reference Laboratory). Methodological differences mean that results are not directly comparable to those from Wyeth Lederle Laboratories (see Clinical Expert Report).

GMTs (μg/mL) immediately before immunisation and 4 weeks later were:

	Meningitec 2 μg	**Meningitec 10 μg**
	GMC (95% CI)	**GMC** (95% CI)
Primary course	**n = 47**	**n = 48**
Pre Dose 1 *age 2 months*	**0.34** (0.24, 0.47)	**0.31** (0.21, 0.47)
1 month post Dose 1 *age 3 months*	**3.43** (2.66, 4.43)	**4.78** (3.56, 6.43)
1 month post Dose 2 *age 4 months*	**7.66** (6.25, 9.38)	**15.82** (13.05, 19.18)
1 month post Dose 3 *age 5 months*	**10.28** (8.72, 12.12)	**18.62** (16.02, 21.64)
9 months post Dose 3 *age 13 months*	**1.24** (0.96, 1.59)	**2.28** (1.86, 2.80)

Numbers (percentages) of children with IgG levels considered protective were:

Group:	**Meningitec 2 µg**	**Meningitec 10 µg**
	% (95% CI)	**%** (95% CI)
Primary course	**n = 47**	**n = 48**
Pre Dose 1 *age 2 months*		
≥ 1 µg/mL	**17%** (8%, 31%)	**24%** (13%, 39%)
≥ 2 µg/mL	**4%** (0.5%, 15%)	**7%** (1%, 18%)
≥ 4 µg/mL	**4%** (0.5%, 15%)	**4%** (0.5%, 15%)
1 month post Dose 1 *age 3 months*		
≥ 1 µg/mL	**96%** (86%, 99%)	**95%** (84%, 99%)
≥ 2 µg/mL	**70%** (55%, 83%)	**76%** (60%, 88%)
≥ 4 µg/mL	**45%** (30%, 60%)	**63%** (47%, 78%)
1 month post Dose 2 *age 4 months*		
≥ 1 µg/mL	**100%** (92%, 100%)	**100%** (93%, 100%)
≥ 2 µg/mL	**100%** (92%, 100%)	**100%** (93%, 100%)
≥ 4 µg/mL	**83%** (69%, 92%)	**100%** (93%, 100%)
1 month post Dose 3 *age 5 months*		
≥ 1 µg/mL	**100%** (93%, 100%)	**100%** (92%, 100%)
≥ 2 µg/mL	**100%** (93%, 100%)	**100%** (92%, 100%)
≥ 4 µg/mL	**92%** (80%, 98%)	**100%** (92%, 100%)
9 months post Dose 3 *age 13 months*		
≥ 1 µg/mL	**67%** (52%, 81%)	**94%** (83%, 99%)
≥ 2 µg/mL	**28%** (16%, 44%)	**58%** (43%, 72%)
≥ 4 µg/mL	**11%** (4%, 24%)	**21%** (11%, 35%)

SBA against the C11 strain was measured at Manchester Public Health Laboratory. GMTs (as reciprocal GMT of final dilution yielding ≥ 50% killing) were:

	Meningitec 2 μg	**Meningitec 10 μg**
	GMT (95% CI)	**GMT** (95% CI)
Primary course	n = 47	n = 48
Pre Dose 1	**1.25**	**1.37**
age 2 months	(0.96, 1.62)	(1.04, 1.82)
1 month post Dose 1	**25.53**	**30.42**
age 3 months	(13.98, 46.65)	(16.00, 57.82)
1 month post Dose 2	**519.95**	**816.84**
age 4 months	(337.70, 800.55)	(548.73, 1215.97)
1 month post Dose 3	**1086.22**	**1155.19**
age 5 months	(754.33, 1564.13)	(834.14, 1599.80)
9 months post Dose 3	**19.85**	**11.82**
age 13 months	(10.72, 36.77)	(6.20, 22.51)

Percentages achieving titres ≥ 1:8 were:

	Meningitec 2 μg	**Meningitec 10 μg**
	% ≥ 1:8 (95% CI)	**% ≥ 1:8** (95% CI)
Primary course	n = 47	n = 48
Pre Dose 1	**4%**	**7%**
age 2 months	(0.5%, 14%)	(1%, 18%)
1 month post Dose 1	**74%**	**68%**
age 3 months	(59%, 86%)	(52%, 82%)
1 month post Dose 2	**100%**	**100%**
age 4 months	(92%, 100%)	(92%, 100%)
1 month post Dose 3	**100%**	**100%**
age 5 months	(93%, 100%)	(92%, 100%)
9 months post Dose 3	**67%**	**50%**
age 13 months	(51%, 80%)	(35%, 65%)

Thus, the 10 μg dose resulted in significantly greater antibody concentrations at 5 months post dose 3 than the 2 μg dose. However, SBA analyses showed no significant differences between the two doses.

Children who completed this study were randomised to receive a booster immunisation with an unconjugated AC polysaccharide meningococcal vaccine at age either 18-24 months or 4 years. Immunogenicity results are presented for 40 children who received the booster at age 15 to 21 months. Again these analyses were performed at the Manchester Public Health Laboratory and are not directly comparable with the results from the Wyeth Lederle Laboratories.

GMTs (μg/mL) immediately before immunisation and 4 weeks later were:

Original Vaccine:	**Meningitec 2 μg**	**Meningitec 10 μg**
	GMC (95% CI)	**GMC** (95% CI)
Booster (Unconjugated AC polysaccharide)	**n = 22 Pre, 23 Post**	**n = 16 Pre, 17 Post**
Pre Booster	**1.15** (0.80, 1.66)	**2.22** (1.47, 3.34)
4 weeks post Booster	**18.96** (15.04, 23.91)	**12.54** (8.84, 17.79)

Numbers (percentages) of children with IgG levels considered protective were:

Original Vaccine:	**Meningitec 2 μg**	**Meningitec 10 μg**
	% (95% CI)	**%** (95% CI)
Booster (Unconjugated AC polysaccharide)	**n = 22 Pre, 23 Post**	**n = 16 Pre, 17 Post**
Pre Booster		
≥ 1 μg/mL	**73%** (50%, 89%)	**88%** (62%, 98%)
≥ 2 μg/mL	**23%** (8%, 45%)	**63%** (35%, 85%)
≥ 4 μg/mL	**5%** (0.1%, 23%)	**19%** (4%, 46%)
4 weeks post Booster		
≥ 1 μg/mL	**100%** (85%, 100%)	**100%** (81%, 100%)
≥ 2 μg/mL	**100%** (85%, 100%)	**100%** (81%, 100%)
≥ 4 μg/mL	**100%** (85%, 100%)	**100%** (81%, 100%)

SBA (C11 strain) GMTs (performed and expressed as above) were:

	Meningitec 2 μg	**Meningitec 10 μg**
	GMT (95% CI)	**GMT** (95% CI)
Booster (Unconjugated AC polysaccharide)	**n = 20 Pre, 22 Post**	**n = 16 Pre, 17 Post**
Pre Booster	**16.00** (6.68, 38.35)	**11.82** (3.56, 39.17)
4 weeks post Booster	**580.77** (322.09, 1047.20)	**266.65** (104.33, 681.56)

Percentages achieving titres ≥ 1:8 were:

	Meningitec 2 μg	**Meningitec 10 μg**
	% ≥ 1:8 (95% CI)	**% ≥ 1:8** (95% CI)
Booster (Unconjugated AC polysaccharide)	**n = 20 Pre, 22 Post**	**n = 16 Pre, 17 Post**
Pre Booster	**70%** (46%, 88%)	**56%** (30%, 80%)
4 weeks post Booster	**100%** (85%, 100%)	**94%** (71%, 99.9%)

The non-conjugated meningococcal AC vaccine increased IgG levels to those thought to be protective in both Meningitec dose groups. Thus, immunisation with conjugated vaccine in infancy resulted in immunological memory, as demonstrated by the responses to subsequent antigen challenge.

II.2.3 Study No D124 P3 Dose determination

The primary objective of this ongoing study is to determine whether immunisation with the applicant's conjugated pneumococcal vaccine protects against nasopharyngeal colonisation and reduces the attack rates for otitis media. However, interim immunogenicity results are presented for 90 infants who received three doses of Meningitec, either **2 μg** (Batch 7-5026-001A) or **10 μg** (Batch 7-5019-008A), at 2, 4 and 6 months of age.

- One month after the third dose, GMTs (assayed at Wyeth Lederle Laboratories) were 1.88 μg/mL (n = 40, 95% CI: 1.47, 2.40) for the 2 μg dose and
- 7.37 μg/mL (n = 50, 95% CI: 6.18, 8.78) for the 10 μg dose.

Numbers of infants with given antibody levels at this time were:

Group:	**Meningitec** 2 μg **(n = 40)**		**Meningitec** 10 μg **(n = 40)**	
	n	**%** (95% CI)	n	**%** (95% CI)
Post				
≥ 1 μg/mL	29	**72%** (58%, 86%)	50	**100%** (96%, 100%)
≥ 2 μg/mL	22	**55%** (40%, 70%)	50	**100%** (96%, 100%)
≥ 4 μg/mL	9	**22%** (10%, 35%)	43	**86%** (76%, 96%)

Both the doses, 2 μg and 10 μg give a good response in terms of immunogenicity. The 10 μg dose produces a faster rise with significantly higher antibodies at the end of the primary series, and a higher sustained level of antibody during the second year of life. Both doses were found to result in an excellent response on boosting with unconjugated polysaccharide antigen.

III. IMMUNOGENICITY

III.1 Controlled Trials in Infants Age less than 12 Months

III.1.1 Study No D110 P500 Plus DTP/Hib at 2, 3 and 4 months

Meningitec was administered concurrently with DTP (Trivac) and Hib (HibTITER) vaccines to 124 infants, while 124 received Engerix B with the other vaccines. Blood samples were taken prior to the first immunisation and at one month after the last immunisation. Five were withdrawn from the study, three at parent's request (one Meningitec, one Engerix B) and two because of adverse events (one from each group). Post vaccine blood samples were missing for a further six patients.

GMTs (ELISA at Wyeth Lederle Vaccines) were as follows:

Group:	**Meningitec (n = 116)**		**Engerix B (n = 121)**		***p***
	GMC (95% CI)	range *(p Post/Pre)*	**GMC** (95% CI)	Range *(p Post/Pre)*	*between groups*
Meningococcal C *(μg/mL)*					
Pre	**0.13** (0.10, 0.17)	0.05-43.36	**0.17** (0.12, 0.22)	0.05-14.79	*0.26*
Post	**23.93** (21.47, 26.68)	5.22-79.26 *(<0.001)*	**0.10** (0.08, 0.12)	0.05-9.84 *(<0.001)*	*<0.001*
Hib *(μg/mL)*					
Pre	**0.17** (0.14, 0.21)	0.05-4.06	**0.15** (0.12, 0.19)	0.05-8.81	*0.53*
Post	**9.83** (7.53, 12.92)	0.19-127.2 *(<0.001)*	**3.90** (2.98, 5.06)	0.05-9.84 *(<0.001)*	*<0.001*
Diphtheria *(IU/mL)*					
Pre	**0.01** (0.01, 0.01)	0.001-0.81	**0.01** (0.01, 0.01)	0.001-1.01	*0.58*
Post	**1.77** (1.53, 2.02)	0.24-19.3 *(<0.001)*	**1.07** (0.94, 1.24)	0.15-7.90 *(<0.001)*	*<0.001*
Tetanus *(IU/mL)*					
Pre	**0.50** (0.41, 0.61)	0.009-4.11	**0.55** (0.44, 0.68)	0.02-12.72	*0.55*
Post	**5.81** (5.02, 6.59)	0.61-41.12 *(<0.001)*	**6.39** (5.64, 7.37)	0.73-50.10 *(<0.001)*	*0.24*

Percentages of children with IgG levels considered protective were:

Group:	**Meningitec (n = 116)**		**Engerix B (n = 121)**		***p***
	n	**%** (95% CI)	n	**%** (95% CI)	*Between groups*
Meningococcal C					
Pre					
≥ 1 µg/mL	16	**14%** (8%, 22%)	23	**19%** (13%, 27%)	*0.3*
≥ 2 µg/mL	7	**6%** (3%, 12%)	7	**12%** (7%, 20%)	*0.1*
Post					
≥ 1 µg/mL	116	**100%** (96%, 100%)	8	**7%** (3%, 14%)	*<0.001*
≥ 2 µg/mL	116	**100%** (96%, 100%)	5	**4%** (2%, 10%)	*<0.001*
Hib					
Pre					
≥ 0.15 µg/mL	57	**49%** (40%, 58%)	52	**43%** (34%, 52%)	*0.36*
≥ 1 µg/mL	11	**9%** (5%, 16%)	11	**9%** (5%, 16%)	*>0.99*
Post					
≥ 0.15 µg/mL	116	**100%** (96%, 100%)	119	**99%** (95%, 100%)	*>0.99*
≥ 1 µg/mL	109	**94%** (88%, 97%)	93	**78%** (69%, 84%)	*<0.001*
Diphtheria					
Pre					
≥ 0.01 IU/mL	47	**41%** (32%, 51%)	52	**43%** (34%, 52%)	*0.79*
Post					
≥ 0.01 IU/mL	116	**100%** (96%, 100%)	120/120	**100%** (96%, 100%)	*0.79*
Tetanus *(IU/mL)*					
Pre					
≥ 0.01 IU/mL	115	**99%** (94%, 100%)	52	**43%** (34%, 52%)	*0.79*
Post					
≥ 0.01 IU/mL	116	**100%** (96%, 100%)	121	**100%** (96%, 100%)	

Acceptable increments in antibody titres were also seen for pertussis.

In comparison with the Engerix B group, there appeared to be an enhanced response to Haemophilus and diphtheria antigens in the Meningitec group, which was ascribed to the common elements shared by the three vaccines.

III.1.2 Study No D118 P3 Plus routine vaccines at 2, 4 and 6 months and a booster dose at 12-15 months

The primary objective of this study was to assess the safety and immunogenicity of the applicant's heptavalent pneumococcal vaccine, which is also conjugated with CRM_{197}. However, Meningitec 10 μg (lot number K-2-4-F05) was administered to the control arm infants together with diphtheria, tetanus and pertussis vaccine at a separate site and oral polio vaccine.
At the time of the booster dose, children were further randomised to receive concomitantly either a Hib conjugate vaccine or MMR.

GMTs (ELISA at Wyeth Lederle Vaccines) were:

Group:	**Meningitec**	**7-valent pneumococcal**
	GMC (95% CI)	**GMC** (95% CI)
Primary course	**n = 96**	
Pre Dose 1 *age 2 months*	**0.09** (0.07, 0.11)	**0.08** (0.06, 0.11)
2 months post Dose 2 *age 6 months*	**2.82** (2.32, 3.43)	**0.07** (0.06, 0.08)
1 month post Dose 3 *age 7 months*	**3.72** (3.25, 4.27)	**0.07** (0.06, 0.08)
Booster	**n = 61**	**n = 53**
1 month post Dose 3 *age 7 months*	**3.46** (2.93, 4.08)	**0.08** (0.07, 0.10)
Pre-booster *age 12-15 months*	**0.55** (0.44, 0.68)	**0.11** (0.08, 0.14)
1 month post booster *age 13-16 months*	**8.03** (7.53, 12.92)	**0.10** (0.08, 0.12)

Numbers (percentages) of children with IgG levels considered protective were:

Group:	**Meningitec**	**7-valent pneumococcal**
	% (95% CI)	**%** (95% CI)
2 months post Dose 2	**n = 96**	**n = 90**
≥ 1 μg/mL	**88%** (79%, 94%)	**1%** (0%, 6%)
≥ 2 μg/mL	**69%** (59%, 99%)	**0%** (0%, 4%)
≥ 4 μg/mL	**37%** (27%, 48%)	**0%** (0%, 4%)
1 month post Dose 3		
≥ 1 μg/mL	**88%** (79%, 94%)	**1%** (0%, 6%)
≥ 2 μg/mL	**69%** (59%, 99%)	**0%** (0%, 4%)
≥ 4 μg/mL	**37%** (27%, 48%)	**0%** (0%, 4%)

Seroconversion rates following DT, OPV, and were similar between the two groups.

Following the booster, the GMT for antibody to serogroup C meningococcus was 1.79-fold higher in the MMR subgroup compared with the Hib subgroup (p = 0.003), but there were no significant differences in the percentages of children achieving presumptively protective levels.

SBA GMTs against the Group C meningococcus (as reciprocal GMT of final dilution yielding ≥ 50% killing) and % children achieving titres ≥ 1:8 were:

Group:	**Meningitec**	**7-valent pneumococcal**
Primary course	n = 30	n = 15
Pre first dose *age 2 months*		
GMT	**3.6**	**1.1**
% ≥ 1:8	**30%**	**0%**
1 month post Dose 3 *age 7 months*		
GMT	**463**	**1.1**
% ≥ 1:8	**100%**	**0%**
Booster	n = 48 pre, 49 post	n = 15
Pre-booster *age 12-15 months*		
GMT	**26**	**3.3**
% ≥ 1:8	**79%**	**27%**
1 month post booster *age 13-16 months*		
GMT	**2341**	**3.1**
% ≥ 1:8	**100%**	**27%**

Responses to MMR and Hib vaccines were similar between the meningococcal and pneumococcal vaccine groups, and did not differ from expected values.

III.1.3 Study No D118 P7A 2, 4 and 6 months; booster at 12-15 months

The study compared the safety and immunogenicity of the applicant's heptavalent pneumococcal vaccine (as above) with Meningitec, with 2:1 randomisation, in 238 infants and 173 at 12-15 months of age. For the primary course half the patients in each group were randomised to receive HBV concurrently and half at least 2 weeks after the test vaccine, while DTP and Hib were given concomitantly.
For the booster dose a further randomisation at a ratio of 3:3:2 compared the outcome for the test vaccine with DTaP and Hib given one month before, concomitantly, or one month after the test vaccine.

GMTs (ELISA at Wyeth Lederle Vaccines) were:

Group:	**Meningitec**	**7-valent pneumococcal**
	GMC	**GMC**
Primary course	**n = 82**	**n = 156**
Pre Dose 1 *age 2 months*	**0.09**	**0.12**
1 month post Dose 3 *age 7 months*	**3.93**	**0.09**

Numbers (percentages) of children with IgG levels considered protective were:

Group:	**Meningitec**	**7-valent pneumococcal**
	%	**%**
Primary course	**n = 82**	**n = 156**
1 month post Dose 3 *age 7 months*		
≥ 1 μg/mL	**98%**	**3.2%**
≥ 2 μg/mL	**82%**	**1.9%**
≥ 4 μg/mL	**48%**	**0.6%**

All 41 infants who received three doses of Meningitec and hepatitis B vaccine concurrently for the primary series achieved adequate titres (≥ 10 mIU/mL) of antibodies against the hepatitis antigen. All 80 infants who received three doses of Meningitec and OPV concurrently for the primary series achieved adequate titres (≥ 1:10) of antibodies against each of the three polioviruses types.

The antibody response to the Meningitec booster was lower when given concomitantly with DTaP and Hib than when given alone.

Group:	**Meningitec alone**	**Meningitec plus**	**7-valent pneumococcal**
1 month post booster *age 13-16 months*	**n = 24**	**n = 25**	**n = 112**
GMC (μg/mL)	**7.71**	**3.14**	**0.08**
≥ 1 μg/mL	**100%**	**88%**	**0%**
≥ 2 μg/mL	**100%**	**80%**	**0%**
≥ 4 μg/mL	**79%**	**40%**	**0%**

However, there were no statistically significant differences between the two Meningitec groups for GMTs of antibody against DTaP and Hib.

III.1.4 Study No D110 P501 Bridging study to manufacturing scale batches

Infants aged 7-10 weeks were randomised to receive three doses of Meningitec batches **either** 7-5036-04A (manufacturing scale batch) **or** 7-5036-01A (pilot batch), at 2, 3 and 4 months of age. Infants received concomitantly mixed DTwP/Hib (Hiberix and Trivax) vaccine 0.5 mL in the opposite thigh.

IgG GMTs and SBA one month after the third dose were measured at the National Reference Meningococcal Laboratory, Manchester, UK. IgG responses to the concomitant Hib vaccine were assayed by ELISA at Wyeth Lederle Laboratories.

Group:	**Meningitec Lot 7-5036-04A** Manufacturing scale	**Meningitec Lot 7-5036-01A** Pilot
	n = 85	**n = 83**
Pre		
GMC µg/mL	**0.15**	**0.18**
Range	0.05-4.06	0.05-14.0
95% CI	0.11, 0.20	0.13, 0.25
No. ≥ 1.0 µg/mL	10/83	15/83
%	**12%**	**18%**
95% CI	6%, 20%	33%, 71%
No. ≥ 2.0 µg/mL	4/83	7/83
%	**5%**	**8%**
95% CI	4%, 16%	33%, 71%
No. ≥ 4.0 µg/mL	2/83	1/83
%	**2%**	**1%**
95% CI	0%, 8%	33%, 71%
Post Dose 3		
GMC µg/mL	**22.1**	**16.3**
Range	3.94-79.7	2.25-89.1
95% CI	19.0, 25.7	13.9, 19.0
No. ≥ 1.0 µg/mL	84/84	83/83
%	**100%**	**100%**
95% CI	96%, 100%	96%, 100%
No. ≥ 2.0 µg/mL	84/84	83/83
%	**100%**	**100%**
95% CI	96%, 100%	96%, 100%
No. ≥ 4.0 µg/mL	83/84	80/83
%	**99%**	**96%**
95% CI	94%, 100%	91%, 100%

Serum bactericidal activity against the standard MnC 11 strain was:

Group:	**Meningitec Lot 7-5036-04A** Manufacturing scale	**Meningitec Lot 7-5036-01A** Pilot
	n = 85	**n = 83**
Pre Dose 1		
GMT^{-1}	**2.1**	**2.1**
Range	2-4	2-16
95% CI	2.0, 2.3	2.0, 2.3
No. ≥ 1.8	0/61	1/61
%	**0%**	**2%**
95% CI	0%, 6%	0%, 8%
Post Dose 3		
GMT^{-1}	**473**	**555**
Range	4-4096	4-4096
95% CI	360, 620	399, 773
No. ≥ 1.8	60/61	58/60
%	**98%**	**97%**
95% CI	92%, 100%	90%, 99%

Haemophilus influenzae polysaccharide antibody levels were:

Group:	**Meningitec Lot 7-5036-04A** Manufacturing scale	**Meningitec Lot 7-5036-01A** Pilot
	n = 85	**n = 83**
Pre		
GMC μg/mL	**0.10**	**0.12**
Range	0.02-1.65	0.05-2.29
95% CI	0.08, 0.12	0.09, 0.15
No. ≥ 0.15 μg/mL	24/84	28/82
%	**29%**	**34%**
95% CI	19%, 39%	24%, 45%
No. ≥ 1.0 μg/mL	3/84	3/82
%	**4%**	**4%**
95% CI	1%, 9%	1%, 10%
Post Dose 3		
GMC μg/mL	**1.4**	**1.31**
Range	0.11-26.2	0.05-43.8
95% CI	1.06, 1.85	0.97, 1.78
No. ≥ 0.15 μg/mL	81/85	76/81
%	**95%**	**94%**
95% CI	89%, 98%	86%, 98%
No. ≥ 1.0 μg/mL	49/85	46/81
%	**58%**	**57%**
95% CI	47%, 68%	45%, 68%

Scale up to manufacturing bath size was not been associated with a loss of immunogenicity. The response to Hib vaccine was maintained.

III.2 Uncontrolled Studies in Infants Aged less than 12 Months

III.2.1 Study No D118 P11 Immunogenicity synopsis

The study aimed to characterise the antibody response of infants to the applicant's heptavalent pneumococcal conjugate vaccine. Data were submitted on 101 infants who received three doses of Meningitec at 2, 4 and 6 months of age. Two months after the third dose, the GMT for meningococcal C-specific IgG was 3.97 μg/mL.

Numbers of infants with given antibody levels were:

Group:	**Meningitec (n = 101)**	
	N	**%** (95% CI)
Post		
≥ 1 μg/mL	95	**94%** (89%, 99%)
≥ 2 μg/mL	77	**76%** (68%, 85%)
≥ 4 μg/mL	54	**53%** (44%, 63%)

III.2.2 Study No D110 P502 Vaccine manufactured in Europe.

In order to compare the vaccine manufactured in Europe with that from the USA, 110 infants aged 7-10 weeks received three 0.5 mL doses of Meningitec (Batches 7-5036-06A, manufactured by the Swiss Serum and Vaccine Institute) at 2, 3 and 4 months of age. Infants also received concomitantly mixed DTP/Hib (ACTHIB DTP) vaccine 0.5 mL in the left thigh.
ELISAs and SBA assays were performed at the National Reference Meningococcal Laboratory, Manchester, UK. IgG response to the concomitant Hib vaccine was assayed by ELISA at Wyeth Lederle Laboratories.

	GMC (95% CI)	Range *(p Post/Pre)*
***Meningococcal C** (μg/mL)*		
Pre	**0.2** (0.15, 0.30)	0.05-46.8
Post dose 3	**20.6** (18.0, 23.6)	2.76-91.0 *(<0.001)*
***Hib** (μg/mL)*		
Pre	**0.16** (0.13, 0.21)	0.05-3.33
Post	**3.69** (2.75, 4.93)	0.05-80.6 *(<0.001)*

Numbers (percentages) of children with IgG levels considered protective were:

	n	**%** (95% CI)
Meningococcal C		
Pre		
≥ 1 μg/mL	19	**19%** (12%, 28%)
≥ 2 μg/mL	9	**9%** (5%, 16%)
Post Dose 3		
≥ 1 μg/mL	98	**100%** (96%, 100%)
≥ 2 μg/mL	98	**100%** (96%, 100%)
Hib		
Pre		
≥ 0.15 μg/mL	34	**40%** (29%, 51%)
≥ 1 μg/mL	10	**12%** (6%, 20%)
Post		
≥ 0.15 μg/mL	90	**98%** (93%, 100%)
≥ 1 μg/mL	78	**85%** (76%, 91%)

Serum bactericidal activity was:

	GMT (95% CI)	Range *(p Post/Pre)*
***MnC 11** (standard strain)*		
Pre	**3.0** (2.1, 4.3)	2-2048
Post dose 3	**596.3** (387.5, 917.7)	2-8192 *(<0.001)*
***MnC 629** (recent UK strain)*		
Pre	**2.8** (2.0, 4.1)	2-2048
Post	**613.1** (390.3, 963.2)	2-8192 *(<0.001)*

Thus, the immunogenicity of the vaccine appears to have been maintained following transfer of manufacture from the USA to Europe.

III.2.3 Study D118P8 Co-administration with wP or aP and OPV or IPV

This blinded, US study enrolled infants at 2 months. Randomisation (1:1) was to either the applicant's heptavalent pneumococcal conjugate vaccine (7VPnC) or Meningitec, with injections at 2, 4, 6 and 12-15 months of age.

All subjects received the following vaccines concurrently with study vaccine at 2, 4 and 6 months of age:

- DTwP-Hib (TETRAMUNE) **or** DTaP (ACEL-IMUNE) **and** Hib (HibTITER)
- oral polio vaccine (OPV, ORIMUNE) **or** inactivated polio vaccine (IPV, IPOL)
- Hepatitis B vaccine could also be administered concurrently with the study vaccine at these time points or at least 2 weeks before or after study vaccine.

At 12-15 months, TETRAMUNE or ACEL-IMUNE and HibTITER, MMR and varicella (VARIVAX) vaccines could be administered concurrently with the 12-15 month dose of the study vaccine or at least 2 weeks before or after study vaccine.

Blood samples were obtained from a subset of approximately 400 subjects on a volunteer basis prior to immunisation at 2 months of age, 1 month after the 3rd immunisation, at 12-15 months of age and approximately 1 month after the 4th immunisation. Results are provided for responses to acellular pertussis vaccine, polio and meningococcal antigens in the synopsis.

Comparison of the responses was made with historical controls from Wyeth–Lederle Vaccines and Pediatrics studies D118 P3, D118 P12 and D118 P16.

Responses to acellular pertussis vaccine antigens were compared with subjects in study D118 P12 who received DTaP and Hib at 2, 4 and 6 months of age as shown below:

Antigen	Pre-Dose 1		Post-Dose 3	
	D118 P8 GMC (95% CI)	**Historical Control** GMC (95% CI)	**D118 P8** GMC (95% CI)	**Historical Control** GMC (95% CI)
PT	1.817 (1.240, 2.662)	1.79 (1.37, 2.33)	20.070 (15.837, 25.434)	17.83 (14.93, 21.28)
FHA	9.239 (6.349, 13.445)	5.87 (4.63, 7.43)	56.127 (45.966, 68.533)	46.70 (39.85, 54.74)
Fimbriae 2	0.796 (0.575, 1.103)	0.82 (0.67, 1.00)	4.321 (3.241, 5.761)	4.17 (3.24, 5.37)
r69k	6.605 (4.368, 9.989)	5.34 (4.22, 6.74)	63.331 (50.443, 79.510)	50.9 (41.65, 62.27)

There was no decrease in immunogenicity of acellular pertussis vaccine (as a component of DTaP) when administered concurrently with Meningitec.

Responses to IPV were as follows:

	Pre-Dose 1			**Post-Dose 3**			**Fold Rise**		
Type	N	GMT	95% CI	N	GMT	95% CI	N[a]	GM	95% CI
Type 1	14	7.325	2.144, 25.027	20	15.364	6.440, 36.654	13	1.532	0.17, 13.90
Type 2	14	2.640	1.180, 5.907	20	52.133	29.923, 90.827	13	14.06	3.70, 53.38
Type 3	14	1.301	0.737, 2.300	20	59.814	21.018, 170.225	13	27.07	6.71, 109.21

% Subjects with GMT $\geq$ 10 (Pre-Dose 1 and Post-Dose 3) were:

	Pre-Dose 1			**Post-Dose 3**		
Type	N	Percent	95% CI	N	Percent	95% CI
Type 1	14	57.1%	28.9%, 82.3%	20	75.0%	50.9%, 91.3%
Type 2	14	35.7%	12.8%, 64.9%	20	100%	83.2%, 100.0%
Type 3	14	7.1%	0.2%, 33.9%	20	85.0%	62.1%, 96.8%

% Subjects with GMT $\geq$ 10 (Post-Dose 3) compared to historical controls were:

	Post-Dose 3	
Type	**D118 P8 Percent (95% CI)**	**Historical Control Percent (95% CI)**
Type 1	75.0% (50.9%, 91.3%)	93.59% (85.6%, 97.9%)
Type 2	100% (83.2%, 100.0%)	93.59% (85.6%, 97.9%)
Type 3	85.0% (62.1%, 96.8%)	80.77% (70.2%, 88.9%)

The historical control group were subjects in study D118 P16 who received DTaP and Hib at 2, 4 and 6 months of age; IPV at 2 and 4 months of age; and hepatitis B vaccine at 2 and 6 months of age (maximum number of available samples is 80).

Responses to meningococcal serogroup C antigen when given with DTaP were:

Pre-Dose 1			Post-Dose 3			Fold Rise		
N	**GMC**	**95% CI**	**N**	**GMC**	**95% CI**	**N[a]**	**GM**	**95% CI**
40	0.101	0.072, 0.142	56	8.722	7.289, 10.438	38	84.18	54.42, 130.22

Thus, the primary series produced a statistically significant rise ($p<0.05$) from pre-dose 1 to post-dose 3 in subjects who received three doses of DTaP

Pre-dose 1 and post-dose 3 GMCs compared to a historical control group (subjects in study D118 P3 who received DTwP-Hib and OPV) were:

Pre-Dose 1		Post-Dose 3	
D118 P8 GMC (95% CI)	**Historical Control GMC (95% CI)**	**D118 P8 GMC (95% CI)**	**Historical Control GMC (95% CI)**
0.101 (0.072, 0.142)	0.09 (0.07, 0.11)	8.722 (7.289, 10.438)	3.7 (3.3, 4.3)

The immunogenicity achieved by subjects who received DTaP compared favourably with the historical control subjects who received DTwP.

The proportions of subjects who received DTaP and Meningitec and achieved pre-defined levels of IgG of ≥1µg/mL, ≥2µg/mL, and ≥4µg/mL were:

Defined Level	Post-Dose 3	
	D118 P8 Percent (95% CI)	**Historical Control Percent (95% CI)**
≥ 1µg /mL	100.0% (93.6%, 100.0%)	98% (93%, 100%)
≥ 2µg /mL	98.2% (90.5%, 100.0%)	82% (73%, 89%)

Responses to meningococcal serogroup C antigen when given with IPV were:

Pre-Dose 1		Post-Dose 3	
D118 P8 GMC (95% CI)	**Historical Control GMC (95% CI)**	**D118 P8 GMC (95% CI)**	**Historical Control GMC (95% CI)**
0.099 (0.061, 0.161)	0.09 (0.07, 0.11)	8.438 (5.980, 11.907)	3.7 (3.3, 4.3)

The historical control group were subjects in study D118 P3 who received DTwP-Hib with Meningitec and OPV at 2, 4 and 6 months of age.

	Post-Dose 3	
Defined Level	D118 P8 Percent (95% CI)	Historical Control Percent (95% CI)
≥ 1µg /mL	100.0% (83.2%, 100.0%)	98% (93%, 100%)
≥ 2µg /mL	95.0% (75.1%, 99.9%)	82% (73%, 89%)

The immunogenicity achieved by subjects who received IPV compared favourably with the historical control subjects.

III.3 Uncontrolled Studies for Single Dose in One Year Olds

III.3.1 Study D110 P802 Single dose in toddlers, with boosting.

This UK Department of Health study evaluated a single dose of Meningitec (Batch number 7-5019-011A) at age 12-17 months at the same time as MMR, followed by plain polysaccharide AC vaccine approximately 6 months later. ELISA and SBA assays were performed at the Manchester Public Health Laboratory (National Meningococcal Reference Laboratory).

Responses to the single dose of Meningitec at 12-17 months were:

Meningitec 10 µg	
	% (95% CI)
	n = 68 Pre, 68 Post
Pre	
≥ 1 µg/mL	**9%** (4%, 19%)
≥ 2 µg/mL	**3%** (1%, 11%)
≥ 4 µg/mL	**0%** (-, -)
Post	
≥ 1 µg/mL	**100%** (93%, 100%)
≥ 2 µg/mL	**94%** (85%, 98%)
≥ 4 µg/mL	**82%** (71%, 90%)

SBA (C11 strain) GMTs (reciprocal of final dilution yielding ≥ 50% killing) and % children achieving titres ≥ 1:8 were:

	GMT, Range (95% CI)	**% ≥ 1:8** (95% CI)
	n = 68 Pre, 68 Post	n = 68 Pre, 22 Post
Pre	**2,** 2-32 (2, 3)	**3%** (1%, 11%)
Post	**125,** 2-8192 (79, 199)	**90%** (79%, 95%)

Data (next page) on the response to the booster dose of unconjugated polysaccharide, with comparisons of pre/post results showed that the decreases from post-primary to pre-booster vaccination, and the increases from pre-booster to post-booster vaccination were all statistically significant.

The increases from post-primary to post-booster vaccination assay demonstrated by the SBA results were statistically significant ($p<0.001$ for both assays) while the increases seen in the ELISA assessment were not statistically significant ($p=0.266$).

Time Point	Statistics	ELISA Assay MnC IgG (µg/mL) (N=67)	SBA Against C11 Strain Assay (N=67)	SBA Against C2AP152 Strain Assay (N=67)
Post-primary Vaccination[a]	N	63	63	62
	Geometric Mean	11.0	125	87
	(95% C.I.)	(8.6 to 14.2)	(77 to 204)	(53 to 142)
	Min., Max.	1.5, 157.7	2, 8192	2, 8192
Missing	N	4	4	5
Pre-booster Vaccination [b]	N	63	65	65
	Geometric Mean	2.1	51	43
	(95% C.I.)	(1.7 to 2.7)	(30 to 85)	(27 to 69)
	Min., Max.	0.3, 17.0	2, 4096	2, 2048
Missing	N	4	2	2
Post-booster Vaccination [b]	N	59	62	62
	Geometric Mean	13.5	1001	847
	(95% C.I.)	(10.2 to 18.0)	(698 to 1436)	(631 to 1135)
	Min., Max.	1.2, 448.8	32, 16384	64, 16384
Missing	N	8	5	5

Ratio of Vaccination Assays (Booster Complete Serology Population)

Ratio	Statistics	ELISA Assay MnC IgG (μg/mL) (N=67)	SBA Against C11 Strain Assay (reciprocal dilutions) (N=67)	SBA Against C2AP152 Strain Assay (reciprocal dilutions) (N=67)
Post-booster/Pre-booster vaccination [a]	N	55	60	60
	Geometric Mean Ratio	6.51	20.63	20.39
	(95% C.I.)	(4.57 to 9.26)	(11.60 to 36.69)	(12.27 to 33.90)
	P-value [d]	<0.001	<0.001	<0.001
	n missing	12	7	7
Pre-booster/Post-primary Vaccination [b]	N	59	61	60
	Geometric Mean Ratio	0.19	0.41	0.49
	(95% C.I.)	(0.14 to 0.24)	(0.24 to 0.70)	(0.29 to 0.83)
	P-value [d]	<0.001	0.002	0.010
	n missing	8	6	7
Post-booster/Post-primary Vaccination [c]	N	57	60	59
	Geometric Mean Ratio	1.27	7.91	10.00
	(95% C.I.)	(0.84 to 1.92)	(4.14 to 15.09)	(5.48 to 18.23)
	P-value [d]	0.266	<0.001	<0.001
	n missing	10	7	8

The incidences of subjects with the specified SBA antibody levels pre- and post-booster vaccination were similar for the C11 strain and C2AP152 strain assays. The subjects who did not have a four-fold increase in SBA assay from pre- to post booster vaccination had high titres before challenge (GMT 414 by C11 assay and GMT 384 by C2AP152 assay compared with 51 and 43 for all subjects), reducing the possibility of them showing a four-fold increase.

By the C11 assay, six subjects achieved SBA results of <8 after the primary dose. After the polysaccharide vaccine these subjects achieved titres ranging from 128 to 8192 (GMT 1625). By the C2AP152 assay there were seven such subjects with post polysaccharide titres ranging from 128 to 4096 (GMT 1131). Thus despite the apparently poor response to the primary dose of vaccine, these subjects showed a comparable response to the group as a whole.

III.4 Controlled Trial of Single Dose in Students

III.4.1 Study No D110 P805 Evaluation of immunological tolerance

Meningococcal AC polysaccharide vaccine was given to 190 subjects of aged 18-25 years, who were randomised to receive either Meningitec 10 μg (Batch 7-5019-014A) or a second dose of unconjugated AC polysaccharide vaccine six months later.
The control group of 52 subjects had not previously received either vaccine and were immunised with Meningitec.

ELISA and SBA assays were performed at the Manchester Public Health Laboratory (National Meningococcal reference Laboratory).

Geometric mean meningococcal C IgG concentrations immediately before immunisation and 4 weeks later were:

Group:	**Meningitec 6 months after unconjugated polysaccharide**	**Second dose unconjugated polysaccharide**	**Meningitec in previously unimmunised**
	n = 83	**n = 87**	**n = 49**
Pre			
GMC	**17.4**	**13.8**	**5.0**
Range	2.5-306.5	0.7-363.8	0.3-136.5
95% CI	13.5, 22.3	10.2, 18.6	3.2, 7.9
Post			
GMC	**35.3**	**17.1**	**40.1**
Range	4.0-445.7	0.2-410.7	2.8-248.5
95% CI	28.3, 43.9	12.6, 23.2	29.2, 55.0

Percentages of subjects with antibody levels at specified levels were:

	Meningitec 6 months after unconjugated polysaccharide	**Second dose unconjugated polysaccharide**	**Meningitec in previously unimmunised**
	n = 83	**n = 87**	**n = 49**
Pre			
≥ 1 μg/mL	**100%**	**98%**	**86%**
≥ 2 μg/mL	**100%**	**90%**	**65%**
≥ 4 μg/mL	**90%**	**83%**	**45%**
Post			
≥ 1 μg/mL	**100%**	**99%**	**100%**
≥ 2 μg/mL	**100%**	**94%**	**100%**
≥ 4 μg/mL	**100%**	**86%**	**96%**

SBA (C11 strain - reciprocal GMT of final dilution yielding ≥ 50% killing) and % subjects achieving titres ≥ 1:8 were:

	Meningitec 6 months after unconjugated polysaccharide	**Second dose unconjugated polysaccharide**	**Meningitec in previously unimmunised**
	n = 83	**n = 87**	**n = 49**
Pre			
GMT	**97**	**132**	**5**
Range	2-8192	2-8192	2-1024
95% CI	60, 157	80, 220	3, 8
% ≥ 1:8	**82%**	**86%**	**22%**
Post			
GMT	**663**	**228**	**783**
Range	4-16384	2-8192	8-16384
95% CI	448, 981	142, 367	506, 1210
% ≥ 1:8	**99%**	**93%**	**100%**

Similar results were seen when serum bactericidal activity against an epidemic strain was measured.

Meningitec was significantly more immunogenic than unconjugated meningococcal C polysaccharide when given to subjects previously immunised with the unconjugated polysaccharide.

Comparison with the previously unimmunised control group did not suggest that a previous dose of unconjugated polysaccharide adversely affected the immunogenicity of a subsequent dose of conjugated polysaccharide.

IV. SAFETY

Due to the different age groups and regimens involved, and the differences between trials in the antigens co administered, the safety information is described by trial.

IV.1 Pilot trial in healthy adults (D110 P3)

Numbers and percentages reporting adverse events in the period Days 0 to 3 were:

	Meningitec (n = 15)		**Unconjugated vaccine (n = 15)**	
	Number	%	Number	%
Erythema	0	0%	4	27%
Induration	0	0%	2	13%
Tenderness	5	33%	5	33%
Headache	2	13%	2	13%
Muscle pain	4	27%	2	13%

The local reactogenicity of the single antigen conjugated vaccine appeared to be less than that of the polyvalent unconjugated polysaccharide antigen.

IV.2 Dose Determination in UK infants plus booster

During the primary series, no redness at the meningococcal site was reported for any dose, and swelling was reported only in one child on one occasion, at 24 hours after the second 2 μg dose.

Following the booster dose of unconjugated polysaccharide vaccine, there were no cases of redness or swelling and only two children, one from each dose group, had a fever of ≥ 38°C within 6 days of the booster.

Percentages in each group with systemic reactions within 24 hours were:

	Meningitec 2 μg	**Meningitec 10 μg**	
	Number **%**	Number **%**	
	N = 57	**N = 58**	**n = 57**
Crying more than usual			
Dose 1	35%	45%	
Dose 2	21%	37%	
Dose 3	18%	26%	
Irritable			
Dose 1	56%	71%	
Dose 2	37%	60%	
Dose 3	41%	46%	

Continued….

	Meningitec 2 μg	**Meningitec 10 μg**	
	Number **%**	Number **%**	
	N = 57	**N = 58**	**n = 57**
More sleepy than usual			
Dose 1	40%	45%	
Dose 2	32%	51%	
Dose 3	23%	37%	
Disturbed night			
Dose 1	2%	21%	
Dose 2	12%	12%	
Dose 3	13%	19%	
Less feed/food than usual			
Dose 1	18%	26%	
Dose 2	12%	9%	
Dose 3	7%	16%	
Vomited			
Dose 1	9%	12%	
Dose 2	2%	11%	
Dose 3	4%	7%	
Fever ≥ 38 °Days 0-3			
Dose 1	2%	2%	
Dose 2	0%	6%	
Dose 3	9%	6%	

From the comparative data presented the higher dose appeared to be associated with a higher incidence of irritability and similar symptoms.

IV.3 Controlled Trials in Infants Age less than 12 Months

D110 P500 - infants 2, 3 and 4 months.

Meningitec was administered concurrently with DTP (Trivac) and Hib (HibTITER).
Numbers whose parents reported local reactions occurring during the day of vaccination and the three subsequent days for each injection site were consistently less frequent than seen with DTP plus Hib injection and approximately as frequent as seen with Engerix B (see next page).
Numbers whose parents reported specific systemic reactions, occurring during the day of vaccination and the three subsequent days were either slightly higher in the Meningitec compared with the Engerix B group or very similar between groups.
Two SAEs in the Meningitec group were bowel obstruction and bronchitis/pneumonia. One AE resulted in withdrawal from the Meningitec group - a fever of 40°C - the only recorded fever to exceed 39.1°C.

Group:	**Meningitec (n = 124)**		**Engerix B (n = 124)**	
Site:	Meningitec	DTP and Hib	Engerix B	DTP and Hib
Redness				
Dose 1	42	59	36	52
	34%	**48%**	**31%**	**45%**
Dose 2	44	71	35	56
	37%	**61%**	**31%**	**48%**
Dose 3	46	66	45	63
	41%	**57%**	**40%**	**56%**
Swelling				
Dose 1	7	34	6	24
	6%	**28%**	**5%**	**21%**
Dose 2	9	34	4	23
	8%	**29%**	**4%**	**21%**
Dose 3	7	28	9	20
	6%	**25%**	**8%**	**18%**
Tenderness				
Dose 1	40	52	42	50
	33%	**42%**	**36%**	42%
Dose 2	23	29	21	34
	20%	**25%**	**19%**	**30%**
Dose 3	15	20	16	23
	13%	**18%**	**15%**	**21%**

D118 P3 Infants at 2, 4 and 6 months of age and booster at 12-15 months

Meningitec 10 μg was administered with DTP and OPV in infants and Hib or MMR as toddlers. During the primary course, local reactions were reported consistently less frequently for the Meningitec site than for DTP plus Hib injection, and less frequently also than for the heptavalent pneumococcal vaccine.

Local reactogenicity was reported as follows:

Group:	**Meningitec (n = 106)**		**7-valent Pneumococcal (n = 106)**	
Site:	Meningitec	DTP and Hib	Pneumococcal	DTP and Hib
Erythema				
Dose 1	9/104	28/104	15/103	29/103
	9%	**27%**	**15%**	**28%**
Dose 2	9/98	28/98	25/98	35/98
	9%	**28%**	**26%**	**36%**
Dose 3	8/95	28/95	19/95	27/95
	8%	**29%**	**20%**	**28%**

Group:	**Meningitec (n = 106)**		**7-valent Pneumococcal (n = 106)**	
Site:	Meningitec	DTP and Hib	Pneumococcal	DTP and Hib
Induration				
Dose 1	7/104	26/104	17/103	32/103
	7%	**25%**	**17%**	**31%**
Dose 2	6/98	23/98	15/98	30/98
	6%	**23%**	**15%**	**31%**
Dose 3	6/95	24/95	12/95	26/95
	6%	**24%**	**13%**	**27%**
Tenderness				
Dose 1	21/104	45/104	22/103	37/103
	20%	**43%**	**21%**	**36%**
Dose 2	15/98	21/98	26/98	29/98
	15%	**21%**	**27%**	**30%**
Dose 3	15/95	24/95	20/95	24/95
	16%	**25%**	**21%**	**25%**

Following the booster injection, local reactions were consistently less frequent than seen with the pneumococcal vaccine and differed little in frequency from those seen with Hib or MMR.

Group:	**Meningitec (n = 63)**		**7-valent Pneumococcal (n = 58)**	
Site:	Meningitec	Hib or MMR	Pneumococcal	Hib or MMR
Erythema	3/63	3/63	13/58	7/58
	5%	**5%**	**22%**	**12%**
Induration	1/63	2/63	9/58	5/58
	2%	**3%**	**16%**	**9%**
Tenderness	6/63	4/63	9/58	7/58
	10%	**6%**	**16%**	**12%**

Numbers of infants and toddlers whose parents reported specific systemic reactions, occurring during the day of vaccination and the three subsequent days, were very similar between the two conjugate vaccine groups

Two infants in the meningitec group with SAEs experienced seizures 32 days after the second dose and pneumonia 2 days after the second dose. Patients in the Meningitec group who were withdrawn because of AEs had febrile seizures 27 days after the second dose, fever of 40.8°C 13 hours after the third dose, and an episode of persistent crying in the 24 hours following the first dose.

Study D118 P7 Infants 2, 4 and 6 months and booster at 12-15 months

For the primary course, DTP OPV and Hib were given concomitantly and local reactions were reported consistently less frequently for the Meningitec site than for DTP plus Hib injection, but with approximately the same frequency as for the heptavalent pneumococcal vaccine.

Group:	**Meningitec (n = 91)**		**7-valent Pneumococcal (n = 183)**	
Site:	Meningitec	DTP and Hib	Pneumococcal	DTP and Hib
Erythema				
Dose 1	11/91	24/91	32/183	32/183
	12%	**26%**	**17%**	**18%**
Dose 2	15/88	29/88	29/159	46/159
	17%	**33%**	**18%**	**29%**
Dose 3	13/80	19/80	25/160	34/160
	16%	**23%**	**16%**	**22%**
Induration				
Dose 1	13/91	18/91	19/183	34/183
	14%	**20%**	**10%**	**19%**
Dose 2	8/88	23/88	18/159	32/159
	9%	**26%**	**11%**	**20%**
Dose 3	10/80	12/80	14/160	33/160
	13%	**15%**	**9%**	**21%**
Tenderness				
Dose 1	22/91	27/91	45/183	49/183
	24%	**29%**	**24%**	**27%**
Dose 2	13/88	20/88	33/159	41/159
	15%	**23%**	**21%**	**26%**
Dose 3	11/80	14/80	37/160	44/160
	14%	**18%**	**23%**	**28%**

For the booster dose, for which the reactogenicity results for each vaccine were pooled, irrespective of timing, local reactions were consistently less frequently reported for Meningitec booster than for the pneumococcal booster or the DTaP plus Hib booster.

Vaccine Site:	**Meningitec (n = 60)**	**Pneumococcal (n = 110)**	**DTaP plus Hib (n = 164)**
Erythema	2/60	10/110	10/164
	3%	**9%**	**6%**
Induration	1/60	7/110	6/164
	2%	**6%**	**4%**
Tenderness	1/60	17/110	16/164
	2%	**15%**	**10%**

Numbers whose parents reported specific systemic reactions, occurring within 48 hours of vaccination, were similar between the two groups.

Following the booster systemic reactions within 48 hours of vaccination were:

Vaccine Group:	Meningitec alone (n = 43)	Meningitec + DTaP, Hib (n = 23)	Pneumococcal alone (n = 82)	Pneumococcal + DTaP, Hib (n = 46)	DTaP, Hib alone (n = 105)
Irritability	17/43 **40%**	10/23 **43%**	39/82 **48%**	25/46 **54%**	40/105 **38%**
Loss of appetite	3/43 **7%**	8/23 **35%**	8/82 **10%**	11/46 **24%**	17/105 **16%**
Diarrhoea	5/43 **12%**	6/23 **26%**	14/82 **17%**	11/46 **24%**	12/105 **11%**
Cry 3+ hours	0/43 **0%**	0/23 **0%**	0/82 **0%**	0/46 **0%**	0/105 **0%**
Fever ≥38.0°C	10/43 **23%**	5/23 **22%**	9/82 **11%**	6/46 **13%**	17/105 **16%**

Three children with SAEs had dehydration 47 days after the third dose, and two had elective surgery. No child in the Meningitec group discontinued because of an AE.

D110P501 Scale-up to manufacturing scale batches

Infants received three doses of Meningitec manufacturing scale or pilot batches at one month intervals (2, 3 and 4 months of age). Infants received concomitantly mixed DTwP/Hib (Hiberix and Trivax) vaccine 0.5 mL in the left thigh.

	Meningitec Lot 7-04A Manufacturing	***DTP-Hib***	**Meningitec Lot 7-01A** Pilot	***DTP-Hib***
Dose 1				
Redness	6/99 **6%**	43/101 **43%**	7/98 **7%**	57/100 **57%**
Swelling	6/100 **6%**	41/99 **41%**	9/98 **9%**	42/101 **42%**
Tenderness	20/100 **20%**	40/100 **40%**	21/99 **21%**	44/99 **44%**
Dose 2				
Redness	10/94 **11%**	44/99 **44%**	12/98 **12%**	57/97 **59%**
Swelling	6/97 **6%**	40/98 **41%**	10/98 **10%**	52/97 **54%**
Tenderness	13/97 **13%**	30/97 **31%**	11/97 **11%**	43/97 **44%**
Dose 3				
Redness	13/95 **14%**	46/95 **48%**	22/96 **23%**	56/98 **57%**
Swelling	12/95 **13%**	39/94 **41%**	16/96 **17%**	49/98 **50%**
Tenderness	9/95 **9%**	25/95 **26%**	17/96 **18%**	34/98 **35%**

Systemic reactions were:

	Dose 1		***Dose 2***		***Dose 3***	
Lot:	7-5036-04A	7-5036-01A	7-5036-04A	7-5036-01A	7-5036-04A	7-5036-01A
Decreased appetite	28/97 **29%**	33/100 **33%**	28/90 **31%**	26/101 **26%**	22/95 **23%**	29/97 **30%**
Sleepy	61/98 **62%**	64/101 **63%**	49/95 **52%**	44/101 **44%**	36/96 **38%**	34/97 **35%**
Irritability	63/99 **64%**	66/101 **65%**	57/97 **59%**	71/101 **70%**	48/96 **50%**	55/99 **56%**
Crying	63/99 **64%**	71/100 **71%**	55/97 **57%**	66/101 **65%**	44/96 **46%**	50/99 **51%**
Crying persistently	15/96 **16%**	15/97 **15%**	4/91 **4%**	11/100 **11%**	3/94 **3%**	9/96 **9%**
Feeling unwell	18/94 **19%**	20/96 **21%**	15/90 **17%**	23/100 **23%**	15/93 **16%**	22/96 **23%**
Fever ≥ 38°C	2/87 **2%**	6/93 **6%**	4/79 **5%**	3/89 **3%**	3/77 **4%**	8/83 **10%**

IV.4 Uncontrolled trials in infants less than 12 months

Study D118 P8 2, 4, 6 and 12-15 months of age

Safety data (30/4/98) were presented from children who received either Meningitec or conjugated pneumococcal vaccine, with DTwP or DTaP and Hib, and OPV or IPV.
Local reactions for the primary course in children who received DTwP were:

Group:	**Meningitec (n = 2877)**		**7-valent Pneumococcal (n = 2890)**	
Site:	Meningitec	DTP and Hib	Pneumococcal	DTP and Hib
Erythema				
Dose 1	320/2877	642/2877	359/2890	633/2890
	11%	**22%**	**12%**	**22%**
Dose 2	307/2678	745/2678	389/2725	683/2725
	11%	**28%**	**14%**	**25%**
Dose 3	322/2532	678/2532	386/2538	673/2538
	13%	**27%**	**15%**	**27%**
Induration				
Dose 1	260/2877	684/2877	315/2890	647/2890
	9%	**24%**	**11%**	**22%**
Dose 2	191/2678	648/2678	335/2725	626/2725
	7%	**24%**	**12%**	**23%**
Dose 3	245/2532	588/2532	324/2538	592/2538
	10%	**23%**	**13%**	**23%**
Tenderness				
Dose 1	701/2877	966/2877	801/2890	1041/2890
	25%	**34%**	**28%**	**36%**
Dose 2	483/2678	698/2678	681/2725	823/2725
	18%	**26%**	**25%**	**30%**
Dose 3	457/2532	716/2532	647/2538	828/2538
	18%	**28%**	**26%**	**33%**

Local reactions for the primary course in children who received DTaP were:

Group:	**Meningitec (n = 691)**		**7-valent Pneumococcal (n = 693)**	
Site:	Meningitec	DTaP and Hib	Pneumococcal	DtaP and Hib
Erythema				
Dose 1	45/691	39/691	69/693	46/693
	7%	**6%**	**10%**	**7%**
Dose 2	37/489	53/489	61/526	55/526
	8%	**11%**	**12%**	**10%**
Dose 3	35/337	31/337	58/422	48/422
	9%	**8%**	**14%**	**11%**
Induration				
Dose 1	29/691	30/691	68/693	46/693
	4%	**4%**	**10%**	**7%**
Dose 2	25/489	36/489	63/526	55/526
	5%	**7%**	**12%**	**10%**
Dose 3	26/337	31/337	44/422	44/422
	7%	**8%**	**10%**	**10%**
Tenderness				
Dose 1	123/691	130/691	122/693	109/693
	18%	**19%**	**18%**	**16%**
Dose 2	73/489	76/489	101/526	90/526
	15%	**16%**	**19%**	**17%**
Dose 3	46/337	45/337	62/422	55/422
	12%	**12%**	**15%**	**13%**

Following the booster injection, in the DTwP group:

Group:	**Meningitec (n = 618)**		**7-valent Pneumococcal (n = 599)**	
Site:	Meningitec	DTP and Hib	Pneumococcal	DTP and Hib
Erythema	68/618	138/618	76/599	140/599
	11%	**22%**	**13%**	**23%**
Induration	56/618	122/618	68/599	123/599
	9%	**20%**	**11%**	**21%**
Tenderness	172/618	232/618	218/599	269/599
	28%	**38%**	**36%**	**45%**

Following the booster injection, in the DTaP group were:

Group:	**Meningitec (n = 178)**		**7-valent Pneumococcal (n = 165)**	
Site:	Meningitec	DTaP and Hib	Pneumococcal	DtaP and Hib
Erythema	8/178	7/178	18/165	6/165
	4%	**4%**	**11%**	**4%**
Induration	8/178	6/178	20/165	9/165
	4%	**3%**	**12%**	**5%**
Tenderness	27/178	26/178	38/165	30/165
	15%	**15%**	**23%**	**18%**

Systemic reactions occurring within 48 hours of vaccination, were generally less in the meningococcal group compared with the pneumococcal group when DTwP or DTaP was

coadministered. The reporting rate was also generally lower with the latter vaccine compared with DTwP.

> Of 1069 hospital admissions only three (anaphylaxis and apnoea following Meningitec, febrile seizure following the pneumococcal conjugate vaccine) were considered probably, possibly or definitely related to immunisation. Admission to hospital for seizures was significantly more common following the pneumococcal conjugate vaccine (10) than following Meningitec (2) (relative risk 7, 95%CI 1.1, 158.1): however only one of these episodes occurred within the first three days after immunisation.
> Nine deaths occurred in the Meningitec group (5 sudden infant death syndrome, 2 homicide, 1 meningitis with multiple organisms not including the meningococcus and 1 congenital heart disease) and 8 (4 sudden infant death syndrome, 1 drowning, 1 motor vehicle accident, 1 bronchopulmonary dysplasia and 1 congenital heart disease) in the pneumococcal group. None were thought to be related to immunisation.

Further safety data from this study are included in the applicant's PSUR.

D110 P502 Vaccine manufactured in Europe.

Infants received three doses of Meningitec (Batches 7-5036-06A, manufactured by the Swiss Serum and Vaccine Institute) at 2, 3 and 4 months of age along with mixed DTP/Hib (ACTHIB DTP).
Local reactions rates were lower at the Meningitec site, in keeping with other studies.
Systemic reactions were similar in type and rate to those seen in other studies.

IV.5 Uncontrolled results for single dose at 12-17 months

Study D110 P802

Children received Meningitec and MMR.

	Number	%	
Swelling Days 0-3	7/73	**10%**	**n = 57**
Redness Days 0-3	13/73	**18%**	**n = 57**
Tenderness/pain Days 0-3	5/72	**7%**	**n = 57**
Crying more than usual	2		
Irritable	13		
More sleepy than usual	5		
Disturbed night	5		
Less feed/food than usual	3		
Vomited	1		
Fever $\geq 38^{\circ}$Days 0-3	4	**5%**	

IV.6 Uncontrolled results for single dose at school entry

Study D110 P801

The data presented in the dossier are based on the safety experience up until August 1998, concerning 77 children who received DTP followed 4-6 weeks later by Meningitec or vice versa or both together. Reactions within three days were:

Group:	**Diphtheria tetanus followed by Meningitec (n = 20)**		**Meningitec followed by diphtheria tetanus (n = 25)**		**Meningitec and diphtheria tetanus together (n = 22)**	
Site:	Meningitec	DT	Meningitec	DT	Meningitec	DT
Swelling	10/20 **50%**	5/23 **22%**	3/25 **12%**	8/23 **35%**	2/22 **9%**	10/22 **45%**
Redness	13/20 **65%**	8/23 **35%**	6/25 **24%**	10/23 **43%**	7/22 **32%**	11/22 **50%**
Tenderness pain	10/18 **56%**	14/23 **61%**	7/23 **30%**	11/20 **55%**	5/21 **24%**	9/20 **45%**
Fever ≥38°C	1/20 **5%**	1/23 **4%**	0/25 **0%**	0/23 **0%**	0/22 **0%**	

IV.7 Controlled trial of single dose in students

Study D110 P805.

Local reactions and fever within three days of immunisation were reported as follows:

Group:	**Meningitec 6 months after unconjugated polysaccharide**	**Second dose unconjugated polysaccharide**	**Meningitec in previously unimmunised**
	n = 80	**n = 88**	**N = 40**
Swelling			
Number	14/80	7/88	4/40
%	**18%**	**8%**	**10%**
95% CI	10%, 28%	4%, 16%	3%, 25%
Redness			
Number	33/80	24/88	13/40
%	**41%**	**27%**	**33%**
95% CI	31%, 53%	19%, 38%	19%, 49%
Tenderness or pain			
Number	68/79	73/88	28/40
%	**86%**	**83%**	**70%**
95% CI	76%, 93%	73%, 90%	53%, 83%
Fever			
Number	1/80	0/88	1/40
%	**1%**	**0%**	**3%**
95% CI	0%, 8%		0%, 15%

The safety profile of Meningitec in this student population gave no cause for concern, and in particular there was no evidence that a previous dose of unconjugated polysaccharide vaccine results in more AEs on receiving Meningitec.

V. CLINICAL EXPERT REPORT

The Clinical Expert Report (CER) is a revised version that takes into account the additional information in the updated dossier and in this report, as well as the safety information which is reviewed in the separate appendices.
The CER provides a clear explanation of the assay methodologies and a critical review of the clinical trial data.

VI. SUMMARY OF PRODUCT CHARACTERISTICS

Satisfactory

VII. CONCLUSIONS

- Meningitec elicits satisfactory immunogenicity at a lower antigen dose than the unconjugated vaccine.
- Prior immunisation with Meningitec, as three doses in infants or as a single dose in subjects of at least 12 months, induces immunological memory as shown by an anamnestic response to challenge with the plain or conjugated polysaccharide antigen.
- Prior immunisation with plain polysaccharide vaccine may be successfully followed by Meningitec; this is of relevance to older subjects who may have received a plain polysaccharide vaccine in the past.
- The data do not at present support the need for booster immunisation. It is to be anticipated that ongoing surveillance of disease should, in due time, provide information on long-term protection afforded by the infant primary series and single doses in older subjects.
- The clinical trials suggest that the vaccine may be given concurrently with other commonly used vaccines as listed in the Summary of Product Characteristics without reduction in immunogenicity or increase in reactogenicity for any of the vaccines.
- The reactogenicity and adverse event profile of Meningitec show no evidence of unexpected safety hazards. The SPC was amended as detailed in the variation assessment report attached; a second PSUR is included in the dossier and is currently under evaluation by the RMS.
- The UK's Committee on Safety of Medicines continues to conclude that the risk-benefit relationship for this vaccine is highly favourable.

VIII. FURTHER INFORMATION

Since this assessment report was written and prior to the decentralised procedure, several variations were approved. These have not been incorporated into this report and instead the variation assessment reports are outlined below. All changes are reflected in the current SPC.

Scope	Procedure Number	Type of modification	Date of end of procedure	Approval/ non approval	Assessment report attached (Y/N)
To implement changes from version 1 of the Core Data Sheet for Meningitec with changes to section 4, Clinical Particulars, and section 6, Pharmaceutical particulars, of the SPC.	UK/H/0356/001/W11/R	Type II mutual recognition variation	15/11/2002	Approved	N
To update sections 4.6 (Pregnancy and Lactation) and 5.1 (Pharmacodynamic Properties) of the SPC, regarding the absence of clinical study data for the administration of Meningitec in pregnant women and the conclusion of study D110 P2, involving infants receiving challenge doses of the meningococcal polysaccharide vaccine.	UK/H/0356/001/W16/R	Type II mutual recognition variation	06/10/2003	Approved	N
Class labelling variation to include nephrotic syndrome relapse in section 4.8 of the SPC	UK/H/0356/001/II/030	Type II mutual recognition variation	08 June 05	Approved	
To amend sections 4.2 & 5.1 of the SPC regarding a booster dose, section 4.5 regarding concomitant administration of Prevenar and meningococcal group C conjugate vaccines, both at the request of the MHRA. Additionally to amend sections 4.3 & 4.4 of the SPC concerning febrile illness.	UK/H/0356/001/II/031	Type II mutual recognition variation	29/04/2005	Approved	N
To amend sections 4.2 and 5.1 of the SPC to change the posology of the product to a two-dose schedule.	UK/H/0356/001/II/032	Type II mutual recognition variation	08/06/2005	Approved	N
To modify section 4.5 to provide information on co-administration with Prevenar.	UK/H/0356/001/II/050	Type II mutual recognition variation	08/06/2005	Approved	N
To amend section 4.8 of the SPC to bring in line with version 5 of the core data sheet (to include hypotonic hyporesponsive episode in section 4.8)	UK/H/0356/001/II/051	Type II mutual recognition variation	15 June 06	Approved	

Module 6

Steps taken after the initial procedure:-

Scope	Procedure Number	Type of modification	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached (Y/N)