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) of Meningitec contains:

Neisseria meningitidis (strain C11)

serogroup C oligosaccharide (10 micrograms)

conjugated to *Corynebacterium diphtheriae* CRM_{197} carrier protein (15 micrograms) and

adsorbed on aluminium phosphate (0.125 mg Al^{3+})

For the 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 (see section 5.1).

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 intravenously (see section 4.4). The safety and immunogenicity of administration via the intradermal or subcutaneous routes have not been evaluated.

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 listed in section 6.1.
- 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).

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).

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.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

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.

Meningitec may be administered at the same time (using a different injection site) as any of the following:
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), Prevenar, Prevenar 13 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 the Infanrix Hexa paediatric 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.

In an open label clinical trial that compared separate with concomitant administrations of Meningitec (two doses at 2 and 6 months and a booster dose at approximately 12 months) and Prevenar (pneumococcal conjugate 7-valent vaccine; three doses at 2, 3.5, 6 months and a booster dose at approximately 12 months) there was no evidence of immune interference between the two conjugate vaccines after the primary series or after the booster doses.

In a double-blind randomized clinical trial, all subjects received Meningitec at 2, 4 and 15 months of age co-administered with either Prevenar or Prevenar 13 (each given at 2, 4, 6 and 15 months of age). All subjects also received Infanrix® hexa, DTPa-HBV-IPV / Hib vaccine at 2, 4 and 6 months of age and Infanrix, DTPa-IPV / Hib vaccine at 15 months of age. Comparable proportions of subjects who received Meningitec with Prevenar or Prevenar 13 reached SBA titres at least 1:8 after the second dose and third doses.

4.6 Fertility, 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 section 5.3). 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.

Breast-feeding

The risk-benefit relationship should also be examined before making the decision as to whether to 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 reported adverse reactions such as dizziness and somnolence may affect the ability to drive or operate machinery (see section 4.8).

4.8 Undesirable effects

Within each system organ class, adverse events are listed under headings of frequency, using the following categories: very common (≥1/10); common (≥1/100 and <1/10); uncommon (≥1/1,000 and <1/100); rare (≥1/10,000 and <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Adverse reactions from clinical studies

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.

All age groups

General disorders and administration site conditions:
Very common: Injection site reactions (including redness, swelling and pain/tenderness)
Common: Fever (≥ 38°C)

Infants and toddlers (< 2 years)

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

Adults and children (4 to 60 years)

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 and connective tissue and bone disorders:
Common: Myalgia (adults)

Adverse reactions from post marketing surveillance

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.

The frequencies of adverse reactions from post-marketing surveillance are based on spontaneous reporting rates and have been calculated using number of reports and number of doses distributed.

All age groups

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])

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

Skin and subcutaneous tissue disorders:
Very rare: Rash, urticaria, pruritus, petechiae*, purpura*, erythema multiforme, Stevens-Johnson syndrome

Musculoskeletal and connective tissue disorders:
Very rare: Arthralgia

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

Respiratory, thoracic and mediastinal disorders:Apnoea*, in very premature infants (≤ 28 weeks of gestation).

* see section 4.4

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions preferably through the online reporting option accessible from the IMB homepage. A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via 'freepost'. Alternatively, the traditional post-paid 'yellow card' option may also continue to be used.

FREEPOST
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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 overdoses have also been reported with recommended single doses of Meningitec.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: *Meningococcal vaccines*, ATC code: *J07AH07*

Immunogenicity

No prospective efficacy trials have been performed.

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 group C conjugate vaccines) covering the period from introduction at the end of 1999 to March 2004 demonstrated the need for a booster dose after completion of the primary series (three doses administered at 2, 3 and 4 months).

Within one year of completion of the primary series, vaccine effectiveness in the infant cohort was estimated at 93% (95% Confidence intervals: 67, 99). However, more than one year after completion of the primary series, there was clear evidence of waning protection. Up to 2007 the overall estimates of effectiveness in age cohorts from 1-18 years that received a single dose of meningococcal group C conjugate vaccine during the initial catch-up vaccination programme in the UK range between 83 and 100%. The data show no significant fall in effectiveness within these age cohorts when comparing time periods less than a year or one year or more since immunisation.

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

3 years.

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) with a plunger stopper (latex-free gray butyl rubber) and a protective-tip cap (latex-free gray butyl rubber). Pack sizes of 1 and 10 pre-filled syringes with or without needle, and a multipack of 2 packs of 10 pre-filled syringes without needle.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Nuron Biotech B.V.
Strawinskylaan 1143
Toren 11-C
107XX
Amsterdam
NL

8 MARKETING AUTHORISATION NUMBER

PA 1886/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

The date of first authorisation: 28th September 2007.

Date of last renewal: 24th August 2012

10 DATE OF REVISION OF THE TEXT

May 2014