IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0022/078/001
Case No: 2038688

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

John Wyeth & Brother Limited

Trading as: Wyeth Pharmaceuticals, **Huntercombe Lane South**, **Taplow, Maidenhead**, **Berkshire SL6 0PH**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Meningitec %v/v Suspension for Injection

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **11/07/2007** until .

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Meningitec suspension for injection
Meningococcal group C oligosaccharide conjugate vaccine (adsorbed).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection
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 group 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.

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

- Persons who are hypersensitive to any component of the vaccine.
- Persons who have shown signs of hypersensitivity to any vaccine containing diphtheria toxoid or non-toxic diphtheria toxin protein.
- Persons who have shown signs of hypersensitivity after previous administration of Meningitec.
- Persons suffering from an acute severe febrile illness. As with other vaccines, the administration of Meningitec should be postponed in these persons.

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.

The vial stopper contains dry natural rubber. This may elicit hypersensitivity reactions if handled during vaccine administration by healthcare personnel who have a history of allergy to latex. In addition, hypersensitivity reactions may occur in vaccinees with a history of allergy to latex.

Meningitec will only confer protection against group C of *Neisseria meningitidis* and may not completely prevent meningococcal group 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 neck pain/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 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 alone (D or T), in combination (DT or dT), or in combination with whole cell or acellular Pertussis (DTwP or DTaP); *Haemophilus influenzae* type b (Hib alone or in combination with other antigens) or combined Measles, Mumps, and Rubella (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 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.

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-MCC]) 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 al 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 this 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 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 to immunise during lactation.

4.7 Effects on ability to drive and use machines

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%).

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 group C conjugate vaccine. In most cases meningococcal group 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 group 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-MenCC = investigational 9-valent pneumococcal conjugate vaccine (not licensed) formulated with meningococcal serogroup C conjugate vaccine (which is the active component in Meningitec)
23pnPS = 23-valent pneumococcal polysaccharide vaccine

Immunogenicity of a single primary dose in toddlers
91% of 75 toddlers of 13 months of age developed SBA titres ≥ 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 titres ≥ 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 form 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 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 group 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 at 2°C to 8°C (in a refrigerator). 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 vial (type I glass) with a stopper (butyl rubber). Pack sizes of 1 and 10 vials without syringe/needles. Pack size of 1 vial with a syringe and 2 needles (1 for withdrawal, 1 for injection).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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. The vaccine must be administered immediately after being drawn up into a syringe. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 22/78/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 14 October 2004

10 DATE OF REVISION OF THE TEXT

August 2006