PRODUCT MONOGRAPH

MENINGITEC®

Meningococcal Serogroup C Conjugate Vaccine
(Diphtheria CRM_{197} Protein)

Suspension
For Intramuscular Injection

Therapeutic Classification
Active Immunizing Agent

Nuron Biotech B.V.
Strawinskylaan 1143, Toren 11-C, 1077XX
Amsterdam, The Netherlands

DATE OF PREPARATION: September 10, 2013

Control #: 168241 **Date of Approval: November 13, 2013**

PRODUCT MONOGRAPH

MENINGITEC®

Meningococcal Serogroup C Conjugate Vaccine

(Diphtheria CRM_{197} Protein)

Suspension For Intramuscular Injection

Active Immunizing Agent

PRODUCT MONOGRAPH

MENINGITEC®

Meningococcal Serogroup C Conjugate Vaccine
(Diphtheria CRM_{197} Protein)
Suspension For Intramuscular Injection

Active Immunizing Agent

ACTION AND CLINICAL PHARMACOLOGY

Meningitec® (Meningococcal Serogroup C - CRM_{197} conjugate vaccine) is intended for the prevention of meningitis and/or septicemia caused by *Neisseria meningitidis* serogroup C in infants and older age groups. Meningitec is composed of meningococcal serogroup C oligosaccharides conjugated to a protein carrier, a non-toxic mutant of diphtheria toxin, CRM_{197}. In the final vaccine, aluminum phosphate is used as an adjuvant.

Meningococcal serogroup C infection is a significant public health hazard, causing meningitis and septicemia in all age groups. In Canada, the number of cases of meningococcal disease caused by all serogroups had declined steadily during the period of 1993 to 1999. For example, the incidence was 0.88 cases per 100,000 population in 1997 and 0.57 cases per 100,000 population in 1998. Infants had the highest incidence, with rates of 12.9 and 6.5 cases per 100,000 population in 1997 and 1998, respectively. Most meningococcal disease during that period was caused by serogroups B and C, which were associated with fatality rates of 5.4% and 12.4%, respectively. In 2000, an increase in meningococcal serogroup C disease was noted in Alberta. Since January of 2001, elevated rates of meningococcal serogroup C disease have occurred in Manitoba, Quebec, British Columbia, and Toronto.

Current polysaccharide vaccines have been shown to prevent serogroup C infection in individuals older than 2 years of age for a duration of 3-5 years. Their protective effect is due to their ability to induce bactericidal antibodies specific for the serogroup C capsular polysaccharide. However,

their use is limited mainly to cluster control for two important reasons; polysaccharide vaccines are poorly immunogenic and thus ineffective in the young, and secondly, the immune response to polysaccharide vaccines at any age is restricted by the inability of such vaccines to induce immunological memory. Consequently, protection induced by such vaccines is short lived. When polysaccharides are conjugated to protein carrier molecules and used as vaccines their recognition by the immune system changes fundamentally. Such conjugated vaccines generate immunological memory in vaccine recipients of all age groups.

Clinical trials demonstrated that Meningitec is highly immunogenic and induces protective levels of bactericidal antibodies in a significant number of subjects after vaccination (See Table 1.). Seven clinical trials were performed to evaluate the appropriate vaccination schedule for subjects of different ages. Data from five trials in infants using a 2-, 3-, 4-month schedule or a 2-, 4-, 6-month schedule demonstrated that 98%-100% of the infants developed serum bactericidal antibody (SBA) titers of at least 1:8 one month after the third dose. A booster dose in the second year of life induced an anamnestic response. Currently, the necessity for a booster dose has not been established.

Data from one trial in toddlers and one trial in adults demonstrated that 91%-100% of the subjects developed SBA titers of at least 1:8 one month after receiving a single dose. The antibody titers following one dose of Meningitec were comparable to those following one dose of licensed unconjugated polysaccharide vaccine in the adult subjects.

To evaluate antibody persistence, blood samples were obtained from infants approximately 1 year after they had been vaccinated on a 2-, 4-, 6-month schedule. Seventy-nine percent (79%) of the infants still had SBA titers of at least 1:8.

Unlike unconjugated polysaccharide vaccines, Meningitec has been shown to induce immunologic memory in infants and toddlers. In two studies, low-dose polysaccharide vaccine was administered 6-12 months after primary vaccination with Meningitec to mimic exposure to

natural infection. SBA titers of at least 1:8 were detected in 94% of the infants and 100% of the toddlers. In one of the studies, low-dose polysaccharide vaccine was administered to a second group four years after primary vaccination with Meningitec. SBA titers of at least 1:8 were detected in 95% of the four year old subjects after challenge with low-dose polysaccharide.

Immune tolerance was evaluated in one study in which adult subjects who had been given polysaccharide vaccine 6 months earlier were randomly assigned to receive either Meningitec or a second dose of polysaccharide vaccine. A control group of subjects with no previous exposure to polysaccharide vaccine also received Meningitec. SBA titers of at least 1:8 were detected one month later in 99% of the subjects given Meningitec after polysaccharide vaccine, 93% of the subjects given a second dose of polysaccharide vaccine, and 100% of the control subjects.

Table 1
Immunogenicity 1 Month Following Meningitec
By Study Type

Study Number[a]	Vaccination Schedule (Number Vaccinated)	Serum Bactericidal Antibody Titers ≥1:8 1 Month Post-Vaccination (Number Evaluated)[b]
I. DOSING STUDIES BY AGE GROUP		
A. Primary Immunogenicity in Infants After Three Doses		
D110 P2	2, 3, 4 months (58)	98% (53)
D110 P500	2, 3, 4 months (124)	100% (58)
D110 P501	2, 3, 4 months (205)	98% (121)
D110 P502	2, 3, 4 months (117)	98% (50)
D118 P3	2, 4, 6 months (106)	100% (30)
B. Booster Dose in Toddlers After Primary Immunization at 2, 4, 6 Months		
D118 P3	Single dose (64)	100% (49)
C. Immunogenicity of Single Dose in Toddlers (13 months)		
D110 P802	Single dose (75)	91% (75)
D. Immunogenicity of Single Dose in Adults (18-60 years)		
D110 P3	Single dose	
	Group: Meningitec (15)	100% (15)
	Group: PSV[c] (15)	100% (15)
II. ANTIBODY PERSISTENCE		
A. Persistence of Immunogenicity in Infants After Three Doses[d]		
D118 P3	2,4,6 months (106)	79% (49)

III. OTHER STUDIES		
A. Evidence of Priming by Meningitec in Infants Assessed by PSV Challenge		
D110 P2	Low-dose PSV challenge 1 year after 2, 3, 4 month immunization (17)	94% (17)
D110 P2	Low-dose PSV challenge 4 years after 2, 3, 4 month immunization (22)	95% (22)
B. Evidence of Priming by Meningitec in Toddlers Assessed by PSV Challenge		
D110 P802	Low-dose PSV challenge 6 months after primary immunization (65)	100% (62)
C. Evaluation of Immune Tolerance in Adults (18-25 years)		
D110 P805	Single dose	
	Group: Meningitec after previous PSV (83)	99% (83)
	Group: PSV after previous PSV (85)	93% (85)
	Group: Meningitec no previous PSV (49)	100% (49)

[a]All studies were performed in the United Kingdom, except D118 P3 and D110 P3, which were performed in the United States.
[b]Not all vaccinated subjects were evaluated.
[c] PSV = Polysaccharide vaccine
[d] For evaluation of antibody persistence, analyses were performed approximately 1 year after primary immunization.

Meningitec was introduced into the UK on November 1, 1999. From March 2000, other meningococcal serogroup C conjugate vaccines were introduced. Reductions in cases of serogroup C disease of between 89% and 94% have been observed in all immunized age groups during 2001/02 when compared to 1998/99, before the meningococcal serogroup C vaccine was introduced. Efficacy estimates have been calculated for all immunized cohorts up to end of December 2001. These are as follows: 89% (95% CI: 69%-96%) for the 3 dose course, 87% (95% CI: 69%- 94%) for toddlers vaccinated at 1-2 years, 100% (95% CI: 93%-100%) for pre-schoolers, 95% (95% CI: 87%-97%) for 5-14 year olds and 94% (95% CI: 79%-99%) for 15-17 year olds.

INDICATIONS AND CLINICAL USE

Meningitec (Meningococcal Serogroup C - CRM_{197} conjugate vaccine) is indicated for the active immunization of children from 2 months of age, adolescents and adults, for the prevention of invasive disease caused by *Neisseria meningitidis* serogroup C.

CONTRAINDICATIONS

Meningitec (Meningococcal Serogroup C - CRM_{197} conjugate vaccine) is contraindicated in patients with a known hypersensitivity to any component of the vaccine, including diphtheria toxoid.

Meningitec is contraindicated in patients who have experienced significant neurologic signs or symptoms, or an allergic or anaphylactoid/anaphylactic reaction following a prior dose of meningococcal serogroup C conjugate vaccine.

WARNINGS

Meningococcal serogroup C conjugate vaccine will only confer protection against serogroup C of *Neisseria meningitidis* and may not protect 100% of persons vaccinated. Invasive serogroup C meningococcal disease has been reported in rare cases in subjects adequately immunized for their age. It will not protect against other serogroups of *Neisseria meningitidis* or other organisms that cause meningitis or septicemia.

As with any intramuscular injection, meningococcal serogroup C conjugate vaccine should be given with caution to individuals with thrombocytopenia or any coagulation disorder or to those receiving anticoagulant therapy.

As with all injectable pediatric vaccines, the potential risk of apnea should be considered when administering the primary immunization series to premature infants. The need for monitoring for at least 48 hours after vaccination should be considered for very premature infants (born $\leq$ 30 weeks of gestation).

As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Meningitec should under no circumstances be administered intravenously.

Applies to vial presentation only:
The vial stopper contains dry natural rubber that may cause hypersensitivity reactions when handled by or when the product is injected in persons with known or possible latex sensitivity.

(See AVAILABILITY OF DOSAGE FORM for packaging components).

PRECAUTIONS

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

Minor illnesses, such as mild respiratory infection with or without low-grade fever, are not generally contraindications to vaccination. The decision to administer or delay vaccination because of a current or recent febrile illness depends largely on the severity of the symptoms and their etiology. The administration of meningococcal serogroup C conjugate vaccine should be postponed in subjects suffering from acute severe febrile illness.

Meningococcal serogroup C conjugate vaccine may not protect 100% of the individuals receiving the vaccine.

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

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

Individuals with impaired immune responsiveness whether due to the use of immunosuppressive therapy, a genetic defect, HIV infection, or other causes may have a reduced antibody response to active immunization.

Drug Interactions

Meningococcal serogroup C conjugate vaccine can be administered at the same time as oral polio vaccine, inactivated polio vaccine, hepatitis B vaccine, diphtheria tetanus whole-cell pertussis-Haemophilus influenzae b conjugate vaccine, diphtheria and tetanus toxoids vaccine and acellular pertussis vaccine, diphtheria tetanus vaccine, pneumococcal conjugate vaccine 7-valent, low dose diphtheria and tetanus toxoids vaccine, and measles mumps rubella vaccine, if this fits conveniently in the immunization scheme. There is no data on the concomitant administration of meningococcal serogroup C conjugate vaccine with Varicella vaccine..

Data on concomitant administration of Meningitec with Prevnar (pneumococcal conjugate vaccine 7-valent) have shown no clinically relevant interference in the antibody response to each of the individual antigens when given as primary series vaccinations.

Data for concomitant administration of meningococcal serogroup C conjugate vaccine and DtaP-containing vaccine are derived from a study of concomitant administration of Meningitec with a pediatric combination vaccine (DtaP-HBV-IPV/Hib) and from a study of concomitant administration of Meningitec with DTaP/Hib.

In various studies with different vaccines, concomitant administration of Meningitec with DtaP-containing vaccines has been shown to result in lower SBA GMTs compared to separate

administrations. 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.

Different injectable vaccines should be given at separate injection sites.

Table 2 presents data on the immunological response of infants to concomitant vaccines, as measured one month after the third dose of Meningitec or HBV vaccine.

Table 2

Immunogenicity Following Concurrent Administration of Routine Infant Vaccines With Meningitec

Concomitant Vaccine	Immunogenicity	Immunogenicity Results for concurrently administered vaccine antigens[a]	
		1 Month After Third Dose	Booster Dose
Concurrent DTP, mixed before injection with HbOC (Hib) (Study D110 P500)		N=116	Not Done
Hib capsular polysaccharide	GMC[b] (μg/mL)	9.8	-
	% subjects with ≥ 1.0 μg/mL	94%	
Diphtheria	GMC (IU/mL)	1.8	-
	% subjects with ≥ 1.0 μg/mL	100%	
Tetanus	GMC (IU/mL)	5.8	-
	% subjects with ≥ 1.0 μg/mL	100%	
Pertussis toxin	GMC (U/mL)	4.2	-
	% subjects with ≥ 2-fold increase in titer	19%	
Pertussis FHA[c]	GMC (U/mL)	15.4	-
	% subjects with ≥ 2-fold increase in titer	41%	
Pertussis fimbriae 2	GMC (U/mL)	25.0	-
	% subjects with ≥ 2-fold increase in titer	87%	

Concurrent PRP-T (Hib) and DTP (Study D110 P501)		N=81 (Meningitec Lot A)	Not Done
Hib capsular polysaccharide	GMC[b] (µg/mL)	1.54	-
	% subjects with ≥ 1.0 µg/mL	57%	
		N=85 (Meningitec Lot B)	Not Done
	GMC[b] (µg/mL)	1.51	-
	% subjects with ≥ 1.0 µg/mL	58%	
Concurrent PRP-T (Hib) (Study D110 P502)		N=92	Not Done
Hib capsular polysaccharide	GMC[b] (µg/mL)	3.69	-
	% subjects with ≥ 1.0 µg/mL	84.8%	
Concurrent DTaP[d] and IPV (Study D118 P8)[e]		N=57 [f, g]	Not Done
Pertussis toxin	GMC (U/mL)	20.1	-
	% subjects with ≥ 2-fold increase in titer	80%	
Pertussis FHA	GMC (U/mL)	56.1	-
	% subjects with ≥ 2-fold increase in titer	69%	
Pertussis fimbriae 2	GMC (U/mL)	4.3	-
	% subjects with ≥ 2-fold increase in titer	74%	
Pertussis r69K[h]	GMC (U/mL)	63.3	-
	% subjects with ≥ 2-fold increase in titer	76%	
Polio Type I	% subjects with titer ≥ 1:10	75%	-
Polio Type II	% subjects with titer ≥ 1:10	100%	-
Polio Type III	% subjects with titer ≥ 1:10	85%	
Concurrent HBV, OPV and DTP-HbOC administered for primary series; concurrent HbOC (Hib) and DTaP administered for booster dose (Study D118 P7)		N=80[i]	N=25[j]
Hepatitis B	% subjects with ≥ 10 mIU/mL	100%	Not Done
Polio Type I	% subjects with titer ≥ 1:10	100%	-
Polio Type II	% subjects with titer ≥ 1:10	100%	-
Polio Type III	% subjects with titer ≥ 1:10	100%	-

Diphtheria	GMC (IU/mL)	Not Done	1.79
	≥ 0.1 IU/mL		100%
Tetanus	GMC (IU/mL)	-	21.4
	≥ 0.1 IU/mL		100%
Hib capsular polysaccharide	GMC[b] (μg/mL)	-	224
	% subjects with ≥ 1.0 μg/mL		96.2%
Pertussis toxoid	GMC (U/mL)	-	86.3
	% subjects with ≥ 4-fold increase in titer		64%
Pertussis FHA	GMC (U/mL)	-	16.8
	% subjects with ≥ 4-fold increase in titer		64%
Pertussis fimbriae 2	GMC (U/mL)	-	13.1
	% subjects with ≥ 4-fold increase in titer		88%
Pertussis r69K[h]	GMC (U/mL)	-	86.3
	% subjects with ≥ 4-fold increase in titer		76%

Concurrent DTP-HbOC administered for primary series; concurrent HbOC (Hib) or MMR administered for booster dose (Study D118 P3)		N=95[k]	N=28[l]
Diphtheria	GMC (IU/mL)	0.69	Not Done
	≥ 0.1 IU/mL	99.0%	
Tetanus	GMC (IU/mL)	4.18	-
	≥ 0.1 IU/mL	100%	
Pertussis toxin	GMC (IU/mL)	23.01	-
	% subjects with ≥ 4-fold increase in titer	37.8%	
Pertussis fimbriae 2	GMC (U/mL)	7.51	-
	% subjects with ≥ 4-fold increase in titer	65.1%	
Pertussis FHA	GMC (U/mL)	9.19	-
	% subjects with ≥ 4-fold increase in titer	23.3%	
Pertussis r69K[h]	GMC (U/mL)	32.54	-
	% subjects with ≥ 4-fold increase in titer	59.3%	
Hib capsular polysaccharide	GMC[b] (μg/mL)	5.58	21.6
	% subjects with ≥ 1.0 μg/mL	86.5%	100%

Measles	% subjects seropositive[m]	Not Done	100%
Mumps	% subjects seropositive	-	82%
Rubella	% subjects seropositive	-	89%
Concurrent Diphtheria-tetanus vaccine (DT) in children 3.5 to <6 years of age (Study D110 P801)		Not Done	N=60
Diphtheria	GMC[b] (U/mL)	-	15.51
	≥ 0.1 IU/mL		100%
Tetanus toxoid	GMC[b] (U/mL)	-	14.9 [n, o]
	≥ 0.1 IU/mL		Data Not Available

[a] Results for control groups consisting of the concurrently administered vaccine antigens without Meningitec were not performed in the studies listed below unless otherwise indicated.
[b]GMC = Geometric mean concentration.
[c] FHA = filamentous hemagglutinin
[d]Antibody titers were not performed for diphtheria and tetanus.
[e]Results are also available from a separate study where infants received DTaP without concurrent Meningitec. The schedule for DTaP was the same as used in study D118 P8 (see below).

Immunogenicity results presented for Pertussis antigens (n=67) are 1 Month after the third dose:

Pertussis toxin	GMC (U/mL)	17.8
	% subjects with ≥ 2-fold increase in titer	83%
Pertussis FHA	GMC (U/mL)	46.7
	% subjects with ≥ 2-fold increase in titer	79%
Pertussis fimbriae 2	GMC (U/mL)	4.2
	% subjects with ≥ 2-fold increase in titer	75%
Pertussis pertactin r69K	GMC (U/mL)	50.9
	% subjects with ≥ 2-fold increase in titer	88%

[f] For ≥ 2-fold increase in titer, n=38 for fimbriae 2 and r69K, n=39 for pertussis toxin and FHA.
[g] For Polio Types I, II, and III, n=20.
[h] pertussis r69K = pertactin.
[i] For hepatitis B, n=41.
[j] Booster dose data is also available for a control group where DTaP and HbOC were administered without Meningitec (n=11).
[k]For Pertussis toxin, n=90; for Pertussis fimbriae, n=86; for Pertussis FHA, n=90; for Pertussis pertactin, n=86; for Hib capsular polysaccharide, n=96.
[l] For Hib capsular polysaccharide, n=33.
[m]MMR immunoglobulin G antibodies were measured by an enzyme-linked immunogsorbent assay using Biowhittaker kit and reported as predicted index value, with a value of ≥ 1 being seropositive.
[n]Results reported in Burrage M, Robinson A, Borrow R, et al. Effect of Vaccination with Carrier Protein on Response to Meningococcal C Conjugate Vaccines and Value of Different Immunoassays as Predictors of Protection. Infection and Immunity. 70 (9):4946-54, 2002.
[o]For Tetanus toxoid, n=65.

Pregnancy

Safety during pregnancy has not been established. Meningococcal serogroup C conjugate vaccine is not recommended for use in pregnant women. There is no clinical study data on the use of this vaccine in pregnant women.

(See TOXICOLOGY).

Lactation

Safety during lactation has not been established. It is unknown whether vaccine antigens or antibodies are excreted in human milk.

Pediatric

The safe and effective use of meningococcal serogroup C conjugate vaccine) in children below the age of 2 months has not been established.

Geriatric

Although the vaccine has been studied in adults, studies have not been conducted in adults 65 years or older.

ADVERSE REACTIONS

Adverse reactions reported across all age groups studied:

Psychiatric disorders: Common (≥1 % and <10 %): Irritability

General disorders and administration site conditions: Very common (≥10%): Injection site erythema; injection site swelling; injection site pain/tenderness
Common (≥1 % and <10 %): Fever ≥38°C

Additional reactions reported in infants (first year of life) and toddlers (second year of life):

Psychiatric disorders: Common (≥1 % and <10 %): Crying

Nervous system disorders: Very common (≥10%): Drowsiness; impaired sleeping

Gastrointestinal disorders: Very common (≥10%): Vomiting; diarrhea

Metabolism and Nutrition disorders: Very common (≥10%): Anorexia

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

Nervous system disorders: Very Common (≥10%): Headache (adults 18 to 60 years)
Common (≥1 % and <10 %): Headache (children between 3.5 and 6 years); somnolence

Musculoskeletal, connective tissue and bone disorders: Common (≥1 % and <10 %): Myalgia

Clinical Trials

In all age groups studied, injection site reactions (including redness, swelling and tenderness/pain) were very common. (See Tables 3 and 6). Tenderness/pain was the most frequently reported injection site reaction, occurring in approximately 2 of every 10 infants and toddlers and approximately 6 of every 10 older subjects. However, injection site reactions 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.

Fever of at least 38.0°C was much more common in infants and toddlers (1 of every 3 or 4 subjects) than in older age groups (1 of every 100 subjects). Temperatures did not usually exceed ≥ 39.0° C, particularly in older subjects.

Infants

Table 3 presents the summary of clinical safety data from six studies in infants who received up to three immunizations with Meningitec beginning at the age of 2 months. The reactions listed were the results of specific symptom inquiry by the clinical investigators. Symptoms including crying, irritability, drowsiness, impaired sleeping, anorexia, diarrhea, and vomiting were observed after vaccination, but there was no evidence that these were related to Meningitec rather than to concomitant vaccines, particularly DTP.

Table 3
Summary of All Solicited Local and Systemic Adverse Reactions
Within 4 Days Following Any Dose of Meningitec
(All Clinical Trials in Infants)

Solicited Adverse Reactions[a]	Incidence (No. with Event/No. Doses Evaluated)	
Injection Site		
Pain (Any)	20%	(2058/10548)
Significant (Interfered With Limb Movement)	5%	(492/10548)
Redness/Erythema (Any)	12%	(1263/10724)
Significant (≥ 2.5 cm)	1%	(126/10724)
Swelling/Induration (Any)	8%	(849/10720)
Significant (≥ 2.5 cm)	1%	(148/10720)
Febrile Reactions		
Temperature ≥38.0° C	25%	(2786/10978)
Significant (≥39.1° C)	2%	(192/10978)
Use of Antipyretic Medication	50%	(419/837)
Systemic Reactions		
Increased Crying	70%	(376/537)
Irritability	62%	(6822/11060)
Drowsiness	36%	(4026/11039)
Slept Through Feed	28%	(97/349)
Impaired Sleeping	23%	(2366/10387)
Anorexia	22%	(2423/11049)
Vomiting	14%	(1468/10699)
Diarrhea	10%	(1037/10382)
Unusual High-Pitched Cry	2%	(5/299)
Urticaria	<1%	(82/10531)
Blue Skin Tone	<1%	(5/10232)
Convulsions	<1%	(1/10531)
Prolonged Crying	<1%	(98/10709)
Shortness of Breath	<1%	(29/10531)
Twitching	<1%	(10/10232)
Weak/Lethargic/Limp	<1%	(10/10232)

[a]Infants usually received concurrent routine childhood vaccines, including Diphtheria-Tetanus-Pertussis (whole cell) Vaccine (DTP), Diphtheria-Tetanus-Pertussis (acellular) Vaccine (DTaP), Haemophilus b Conjugate Vaccine (Hib), Hepatitis B Vaccine (HBV), Oral Polio Vaccine (OPV), and/or Inactivated Polio Vaccine (IPV). Local reactions were assessed only at the site of Meningitec injection.

In a randomized, controlled clinical study performed in the United States (Kaiser Study D118 P8), the profile for Meningitec administered at 2, 4, and 6 months of age with concomitant DTP/HIB (Trivax mixed with HibTITER) or DTaP (Acel-Imune) was similar to that observed in other infant studies. (See Tables 4 and 5). The incidence of local reactions was somewhat lower

in the Meningitec recipients than in the control Prevnar® (7-Valent Pneumococcal Conjugate) vaccine recipients. Pain, redness, and swelling were more common after doses of DTP/Hib than after Meningitec or Prevnar doses, whereas these three local reactions occurred with similar frequencies after doses of DTaP and doses of Meningitec. The most frequently reported systemic reactions were irritability, drowsiness, fever, impaired sleeping, and anorexia, which occurred with similar frequency in Meningitec and Prevnar vaccine recipients.

Table 4
Comparative Local Reactogenicity Profile in Infants
Within 4 Days Following Any Dose (Study D118 P8)

Local Reactions[a]	Incidence (No. with Event/No. Doses Evaluated)			
	Meningitec Group		Prevnar Group	
Concurrent DTP/Hib	**Meningitec Site**	**DTP/Hib Site**	**Prevnar Site**	**DTP/Hib Site**
Pain/Tenderness (Any)	20% (1641/8087)	29% (2380/8087)	26% (2146/8153)	33% (2715/8153)
Significant (Interfered with Limb Movement)	5% (424/8087)	7% (595/8087)	8% (628/8153)	10% (792/8153)
Redness (Any)	12% (949/8087)	26% (2065/8087)	14% (1134/8153)	24% (1990/8153)
Significant (≥ 2.5 cm)	1% (94/8087)	4% (305/8087)	1% (113/8153)	4% (324/8153)
Swelling (Any)	9% (696/8087)	24% (1920/8087)	12% (975/8153)	23% (1865/8153)
Significant (≥ 2.5 cm)	2% (128/8087)	6% (512/8087)	3% (214/8153)	7% (531/8153)
Concurrent DTaP	**Meningitec Site**	**DTaP Site**	**Prevnar Site**	**DTaP Site**
Pain/Tenderness (Any)	16% (242/1557)	16% (251/1557)	18% (288/1641)	9% (149/1641)
Significant (Interfered with Limb Movement)	2% (35/1557)	2% (31/1557)	3% (56/1641)	<1% (10/1641)
Redness (Any)	8% (117/1557)	8% (123/1557)	11% (188/1641)	9% (145/1641)
Significant (≥ 2.5 cm)	1% (17/1557)	1% (20/1557)	1% (18/1641)	1% (23/1641)
Swelling (Any)	5% (80/1557)	6% (97/1557)	11% (175/1641)	16% (257/1641)
Significant (≥ 2.5 cm)	<1% (6/1557)	<1% (15/1557)	2% (28/1641)	2% (37/1641)

[a] Local reactions may also have occurred due to concurrent administration of HBV in the same limb as DTP/Hib (Tetramune®) or DTaP (Acel-Imune®), in some subjects.

Table 5
Comparative Systemic Reactogenicity Profile in Infants
Within 4 Days Following Any Dose (Study D118 P8)

Systemic Reactions[a]	Incidence (No. with Event/No. Doses Evaluated)			
	Meningitec		7VPnC	
Irritability	65%	(5378/8328)	70%	(5862/8382)
Drowsiness	36%	(3035/8317)	36%	(3046/8363)
Temperature ≥38.0° C	29%	(2449/8322)	36%	(3019/8370)
Impaired Sleeping	24%	(1981/8317)	26%	(2163/8363)
Anorexia	23%	(1926/8329)	25%	(2094/8375)
Vomiting	14%	(1171/8332)	17%	(1389/8376)
Diarrhea	10%	(861/8327)	11%	(960/8362)
Temperature ≥39.1° C	2%	(171/8322)	3%	(260/8344)
Urticaria	<1%	(69/8334)	<1%	(79/8382)
Prolonged Crying	<1%	(42/8263)	<1%	(50/8305)
Shortness of Breath	<1%	(17/8334)	<1%	(14/8382)
Weak/Lethargic/Limp	<1%	(9/8334)	<1%	(6/8382)
Twitching	<1%	(9/8334)	<1%	(5/8382)
Blue Skin Tone	<1%	(4/8334)	<1%	(5/8382)
Convulsions	<1%	(1/8334)	<1%	(9/8382)
Gray/Ashen Skin Tone	0%	(0/8334)	<1%	(2/8382)

[a] Systemic reactions may also have occurred due to concurrent administration of routine childhood vaccines, including Diphtheria-Tetanus-Pertussis (whole cell) Vaccine (DTP), Diphtheria-Tetanus-Pertussis (acellular) Vaccine (DTaP), Haemophilus b Conjugate Vaccine (Hib), Hepatitis B Vaccine (HBV), Oral Polio Vaccine (OPV), and/or Inactivated Polio Vaccine (IPV).

Toddlers Through Adults

Tables 6 and 7 present analysis of local reactions and systemic reactions, respectively, occurring in toddlers and older subjects after one immunization with Meningitec. Data are pooled from seven studies, representing approximately 1100 subjects. The local and febrile reactions listed for both age groups, and the systemic reactions listed for toddlers, were the results of specific symptom inquiry by the clinical investigators. The systemic reactions listed for older subjects were spontaneously reported to the investigators.

The systemic events commonly reported for toddlers (irritability, impaired sleeping, anorexia, drowsiness) were similar to those reported for infants. Commonly reported systemic events in older subjects included headache, drowsiness, myalgia, and vomiting.

Table 6
Summary of Solicited Local and Febrile Reactions
Within 4 Days Following One Dose of Meningitec in Toddlers and Older Subjects

	Incidence (No. with Event/No. of Doses Evaluated)			
	13-24 months		4-60 years	
Injection Site				
Pain (Any)	21%	(211/991)	63%	(123/196)
Significant (Interfered With Limb Movement)	9%	(83/919)	7%	(1/15)
Redness/Erythema (Any)	9%	(94/992)	36%	(72/202)
Significant (≥ 2.5 cm)	1%	(6/992)	13%	(27/202)
Swelling/Induration (Any)	7%	(73/992)	16%	(33/202)
Significant (≥ 2.5 cm)	2%	(15/992)	7%	(15/202)
Febrile Reactions				
Temperature ≥ 38.0° C	30%	(337/1136)	1%	(3/202)
Significant (≥ 39.1° C)	4%	(41/1136)	0%	(0/202)
Use of Antipyretic Medication	41%	(26/63)	7%	(1/15)

Table 7
Summary of Solicited Systemic Reactions Within 4 Days (Toddlers)
and Unsolicited Systemic Reactions Within 4 Weeks (Older Subjects)
Following One Dose of Meningitec

	Incidence (No. with Event/No. of Doses Evaluated)			
	13-24 months		4-60 years[a]	
Irritability	55%	(635/1165)	2%	(5/237)
Impaired Sleeping	25%	(270/1100)	None	
Anorexia	23%	(270/1162)	1%	(2/237)
Drowsiness/Somnolence	20%	(227/1163)	3%	(7/237)
Diarrhea	11%	(114/1026)	2%	(5/237)
Vomiting	6%	(67/1164)	3%	(7/237)
Increased Crying	3%	(2/73)	None	
Urticaria	1%	(11/1092)	None	
Prolonged Crying	<1%	(4/1086)	None	
Shortness of Breath/Dyspnea	<1%	(1/1092)	1%	(2/237)
Twitching	<1%	(1/1029)	None	
Headache	Not queried		13%	(31/237)
Pharyngitis	Not queried		5%	(12/237)
Myalgia	Not queried		3%	(7/237)
Rhinitis	Not queried		3%	(7/237)
Bronchospasm	Not queried		2%	(5/237)
Dyspepsia	Not queried		2%	(2/237)
Infection Viral	Not queried		2%	(5/237)
Otitis Media	Not queried		2%	(5/237)
Abdominal Pain	Not queried		1%	(2/237)
Infection	Not queried		1%	(2/237)
Malaise	Not queried		1%	(2/237)
Trauma	Not queried		1%	(2/237)
Nausea	Not queried		1%	(2/237)
Upper Respiratory Tract Infection	Not queried		1%	(2/237)

[a]The rates shown are for unsolicited reactions that occurred in 1% or more of subjects.

Children between the ages of 25 months and 47 months were not included as subjects in clinical trials, and therefore no safety information from clinical trials is available for this age group.

Post-Marketing Surveillance (for all age groups)

The frequencies given below are based on spontaneous reporting rates for Meningitec in the UK and have been calculated using number of reports received as the numerator and number of doses of Meningitec distributed as the denominator.

Blood and Lymphatic System Disorders: very rare (<0.01%): Lymphadenopathy

Immune System Disorders: very rare (<0.01%):Anaphylactic/anaphylactoid reaction including shock; hypersensitivity reactions including bronchospasm, facial edema and angioedema.

Nervous System Disorders: very rare (<0.01%): Dizziness; convulsions including febrile convulsions and seizures in patients with pre-existing stable seizure disorder; hypoesthesia and/or paraesthesia ; hypotonia.

General disorders and administration site conditions: very rare (<0.01%): Injection site vesicles; injection site dermatitis; injection site hypersensitivity, including urticaria; injection site induration; injection site inflammation; injection site mass; injection site pruritus.

Musculoskeletal, connective tissue and bone disorders: very rare (<0.01%): Arthralgia.

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

Skin and Subcutaneous Tissue Disorders: very rare (<0.01%): Rash, pruritus, erythema multiforme, Stevens-Johnson syndrome.

Gastrointestinal Disorders: very rare (<0.01%): Nausea, abdominal pain.

There have been very rare spontaneous reports of hypotonia (including hypotonic-hyporesponsive episode [HHE]) 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.

There have been spontaneous reports of very rare petechiae and/or purpura following immunization in the postmarketing experience. Since meningococcal serogroup C conjugate vaccine may not protect against 100% of meningococcal serogroup C disease or disease due to organisms other than *Neisseria meningitidis* serogroup C, individuals who experience petechiae and/or purpura following vaccination should be thoroughly evaluated for the possibility of an infectious or other cause unrelated to vaccination.

As with other pediatric vaccines, there have been spontaneous reports of apnea 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 including diphtheria tetanus pertussis vaccine (DTP), inactivated polio vaccine (IPV), oral polio vaccine (OPV), Haemophilus influenzae type b vaccine (Hib), diphtheria tetanus pertussis - Haemophilus influenzae type b vaccine (DTP-Hib), and/or diphtheria tetanus acellular pertussis - hepatitis B vaccine (DTaP-HBV). In addition, in most of the reports existing medical conditions such as history of apnea, infection, prematurity, and/or seizures were present.

OVER DOSAGE

There have been reports of overdosage with meningococcal serogroup C conjugate vaccine. Most cases have involved inadvertent revaccination at varying intervals following initial vaccination. Most individuals were asymptomatic. Of the events reported, the majority have also occurred with recommended single doses of meningococcal serogroup C conjugate vaccine.

DOSAGE AND ADMINISTRATION

Dosage

The dosage is 0.5 mL given intramuscularly, with care to avoid injection into or near nerves and blood vessels. The vaccine should not be injected in the gluteal area because of the potential risk of injury to the sciatic nerve. The vaccine should not be injected intravenously. Furthermore, the safety and immunogenicity of the intradermal or subcutaneous routes have not be evaluated.

Infants under the age of 12 months:
Two doses, each of 0.5 mL, the first dose given not earlier than 2 months and with an interval of at least 2 months between doses.

For previously unvaccinated children over the age of 12 months, adolescents and adults:
A single dose of 0.5 mL.

Booster Dose:
A booster dose should be given after completion of the primary immunization series in infants. The timing of this dose should be in accordance with official recommendations whenever available and preferably at about 12 months of age. The need for further boosters has not yet been established. 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 (Meningococcal Serogroup C - CRM_{197} conjugate vaccine) is a sterile suspension containing an adjuvant. Shake vigorously immediately prior to use to obtain a uniform suspension in the vaccine container. After shaking, the vaccine is a homogeneous, white suspension. The vaccine should not be used if it cannot be resuspended.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. This product should not be used if particulate matter or discoloration is found.

For the vial presentation, the vaccine is to be administered immediately after being drawn up into a syringe.

The recommended dose is 0.5 mL given intramuscularly. This vaccine should not be injected intradermally, subcutaneously or intravenously since the safety and immunogenicity of these routes have not been evaluated.

The preferred sites are the anterolateral aspect of the thigh in infants or in the deltoid muscle of the upper arm in older children, adolescents and adults. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk and/or blood vessel.

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

Before injection, the skin at the injection site should be cleansed and prepared with a suitable germicide. After insertion of the needle, aspirate and wait to see if any blood appears in the syringe, which will help avoid inadvertent injection into a blood vessel. If blood appears, withdraw the needle, discard the syringe and prepare for a new injection at another site.

PHARMACEUTICAL INFORMATION

Proper name: Meningococcal Serogroup C - CRM_{197} conjugate vaccine
Pharmacotherapeutic Group: *Meningococcal vaccines*, ATC code: *J07AH*

Description

Meningitec (Meningococcal Serogroup C - CRM_{197} conjugate vaccine) is a sterile suspension of the *Neisseria meningitidis* serogroup C oligosaccharide conjugated to *Corynebacterium diphtheriae* CRM_{197} protein. CRM_{197} is a non-toxic variant of diphtheria toxin isolated from cultures of *Corynebacterium diphtheriae* strain *C7(β197)* grown in a casamino acids and yeast-based medium. CRM_{197} is purified through ultra filtration, ammonium sulfate precipitation, and ion-exchange chromatography to high purity.

Composition

Meningococcal serogroup C conjugate vaccine is manufactured as a liquid suspension with composition as described in the following table.

Ingredients		Strength or dosage (label claim)
Active Ingredient		
	Neisseria meningitidis Serogroup C Oligosaccharide	10.0 µg
	Diphtheria, CRM_{197}	15.0 µg
Non-Medicinal Ingredients		
	Sodium chloride	4.25 mg
	Aluminum phosphate	0.5 mg (0.125 mg Al 3+)
	Water for Injection (WFI)	qs 0.5 mL

After shaking, the vaccine is a homogenous white suspension.
The vaccine does not contain a preservative.

Stability and Storage

Meningitec (Meningococcal Serogroup C - CRM_{197} conjugate vaccine) should be stored at 2°C to 8°C (36°F to 46°F). Do not freeze. Discard if the vaccine has been frozen. When stored under labelled condition, Meningitec is stable until the expiration date indicated on the container label.

Keep out of the reach of children.

AVAILABILITY OF DOSAGE FORM

Meningitec (Meningococcal Serogroup C - CRM_{197} conjugate vaccine) is supplied in a pre-filled syringe (type I glass) with a plunger rod (polypropylene) and a plunger stopper (grey butyl rubber). Pre-filled syringes contain 0.5 mL of final product and are available in packages containing ten (10) syringes.

PHARMACOLOGY

Animal Immunogenicity

The primary pharmacodynamic effect of Meningitec (Meningococcal Serogroup C- CRM_{197} conjugate vaccine) is the induction of a humoral antibody response. It has been clearly demonstrated in the mouse (and confirmed in the rabbit) that conjugation of meningococcal serogroup C saccharide to the CRM_{197} carrier protein results in a greatly enhanced immunogenic response. The antibody response has been shown to be dependent on the concentration of

saccharide in conjugate administered; measurement of antibody titers produced at Weeks 4 and 6 following immunization across a dosage range from 0.0032 mg to 10 mg in the mouse demonstrated a clear dose-response relationship.

In addition, a large secondary rise in the antibody response was demonstrated following a second dose of conjugated meningococcal serogroup C oligosaccharide in the mouse and rabbit model. This primary and secondary response was demonstrated (in the mouse only) to be considerably more pronounced than the response to a licenced unconjugated polysaccharide vaccine or to the meningococcal serogroup C saccharide antigen not conjugated to, but in the presence of, the diphtheria CRM_{197} protein. From the results it was reasonable to conclude that immunological memory, presumably dependent on T cells, has been induced by the conjugation of the meningococcal serogroup C oligosaccharide antigen to the carrier protein, diphtheria CRM_{197}.

Administration of conjugate at a range of dose levels in the presence and absence of aluminum phosphate as adjuvant has clearly shown an enhanced antibody response in the presence of adjuvant, the effect being most pronounced at low conjugate dose levels and early in the immune response.

Antibody titers measured in response to the administration of conjugate were reasonably consistent overall, within the limitations of the bioassay system used and were not affected by scale-up of the conjugation technology.

The bactericidal activity of mouse antibodies raised against the meningococcal serogroup C conjugate vaccine was measured using an *in vitro* bactericidal plate assay. Good correlation was seen between bactericidal titers and ELISA IgG titers in mice previously immunised with a range of conjugate vaccine preparations and dilutions indicating that the murine antibodies measured in the ELISA assay possess bactericidal activity.

TOXICOLOGY

Female mice were immunized 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 cesarean 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 fetal mice.

There has been no evidence of local or systemic toxicity in any experiment.

BIBLIOGRAPHY

1 Borrow R, Richmond P, Kaczmarski E, et al. Meningococcal Serogroup C - Specific IgG Antibody Responses and Serum Bactericidal Titres in Children Following Vaccination With a Meningococcal A/C Polysaccharide Vaccine. FEMS Immunol Med Microbiol 2000;28:79-85.

2 Borrow R, Goldblatt D, Andrews N, et al. Antibody Persistence and Immunological Memory at Age 4 Years after Meningococcal Group C Conjugate Vaccination in Children in the United Kingdom. JID 2002;186:1353-1357.

3 Burrage M, Robinson A, Borrow R, et al. Effect of Vaccination with Carrier Protein on Response to Meningococcal C Conjugate Vaccines and Value of Different Immunoassays as Predictors of Protection. Infection and Immunity 2002;70:4946-4954.

4 Canadian Immunization Guide (7th edition, 2006)**.**

5 Daum R, Hogerman D, Rennels M, et al. Infant Immunization With Pneumococcal CRM_{197} Vaccines: Effect of Saccharide Size on Immunogenicity and Interactions with Simultaneously Administered Vaccines. JID 1997;176:445-455.

6 De Wals P, Dionne M, Douville-Fradet N, et al. Impact of a Mass Immunization Campaign Against Serogroup C Meningococcus in the Province of Quebec, Canada. Bull WHO 1996;74(4):407-411.

7 Edwards KM, Rennels MB, Immnunogenicity and Safety of Conjugate Meningococcal Group C Vaccine in Infants. Pediatric Research. 39(4):183A, 1996.

8 Fairly CK, Begg N, Borrow R., et al. Conjugate Meningococcal Serogroup A and C Vaccine: Reactogenicity and Immunogenicity in United Kingdom Infants. J Infect Dis 1996;174:1360-1363.

9 Goldblatt D, Pinto Vas RPJ, Miller E. Antibody Avidity as a Surrogate Marker of Successful Priming by *Haemophilus Influenzae* Type B Conjugate Vaccines following Infant Immunization. J Infect Dis 1998;177:1112-5.

10 Goldschneider I, Gotschlich E, Artenstein M. Human Immunity to the Meningococcus. II. Development of Natural Immunity. J Exp Med 1969;129;1327-1348.

11 Goldschneider I, Gotschlich E, Artenstein M. Human Immunity to the Meningococcus. I. The Role of Humoral Antibodies. J Exp Med 1969;129:1307-1326.

12 Gotschlich E, Goldschneider I, and Artenstein M. Human Immunity to the Meningococcus. IV. Immunogenicity of Group A and Group C Meningococcal Polysaccharides in Human Volunteers. J Exp. Med. 1969;129;1367-1384.

13 Granoff D, Gupta R, Belshe R, Anderson E. Induction of Immunologic Refractoriness in Adults by Meningococcal C Polysaccharide Vaccination. J Infect Dis 1998;178:870-874.

14 Granoff D, Maslanka S, Carlone G, et al. A Modified Enzyme-Linked Immunosorbent Assay for Measurement of Antibody Responses to Meningococcal C Polysaccharide That Correlate With Bactericidal Responses. Clin Diagn Lab Immunol 1998;5(4):479-485.

15 Kimura A, Ginsberg D, Hogerman D, et al. Clinical Evaluation of a Meningococcal Group C Oligosaccharide-CRM_{197} Conjugate (MnC-CRM) Vaccines in Adults. Infectious Disease Society of America, 1995 annual meeting.

16 Mäkelä P, Eskola J, Käyhty H, et al. Vaccines Against *Haemophilus Influenzae* Type B. In "Molecular and Clinical Aspects of Bacterial Vaccine Development" Eds. Ala'Aldeen D, Hormaeche C, pub. Wiley, Chichester 1995;41-91.

17 Maslanka S, Gheesling L, Libutti D, et al. Standardization and a Multilaboratory Comparison of *Neisseria Meningitidis* Serogroup A and C Serum Bactericidal Assays. Clin Diag Lab Immunol 1997;4(2):156-167.

18 Prevnar® Canadian Product Monograph.

19 Ramsay ME, Andrews N, Kaczmarski E, Miller E. Efficacy of a Single Dose of Group C Meningococcal Conjugate vaccine in teenagers and toddlers in England. Lancet 2001;357:195-196.

20 Richmond P, Cartwright K, Borrow R, et al. An Investigation of the Immunogenicity and Reactogenicity of Three Meningococcal Serogroup C Conjugate Vaccines Administered as a Single Dose in UK Toddlers. Eleventh Internal Pathogenic Neisseria Conference. Nice 1998, page 153.

21 Richmond P, Kaczmarski E, Borrow, et al. Meningococcal C Polysaccharide Vaccine Induces Immunologic Hyporesponsiveness in Adults That is Overcome by Meningococcal C Conjugate Vaccine. J Infect Dis 2000;181:761-764

22 Richmond P, Miller, Borrow R, et al. Concise Communication. Meningococcal Serogroup Conjugate Vaccine is Immunogenic in Infancy and Primes for Memory. (Submitted to JID).

23 Squires SG, Pelletier L, Mungai M, Tsang R, Collins F, Stoltz J. Invasive meningococcal disease in Canada, 1 January 1997 to 31 December 1998. Can Commun Dis Rep 2000;26(21):177-82.

24. Tejedor JC, Omenaca F, Garcia-Sicilia J et al. Immunogenicity and reactogenicity of a three-dose primary vaccination course with a combined diphtheria-tetanus-acellular pertussis-hepatitis B inactivated polio-haemophilus influenzae type B vaccine coadministered with a meningococcal C conjugate vaccine. Pediatr Infect Dis J. 2004;23 (12):1109-1115.