AUSTRALIAN PRODUCT INFORMATION
MENVEO (meningococcal (Groups A, C, W-135 and Y) oligosaccharide CRM197) POWDER AND SOLUTION FOR SOLUTION FOR INJECTION

1. NAME OF THE MEDICINE

Meningococcal (Groups A, C, W-135 and Y) Oligosaccharide CRM_{197} Conjugate Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MENVEO powder and solution for solution for injection

MENVEO consists of one vial containing the lyophilised Meningococcal Group A (MenA) Conjugate Component plus excipients, and one syringe or vial containing the liquid Meningococcal Groups C, W-135 and Y (MenCWY) Conjugate Component plus excipients. The reconstituted sterile liquid vaccine is administered by intramuscular injection and contains meningococcal serogroup A, C, W-135 and Y oligosaccharides conjugated individually to *Corynebacterium diphtheriae* CRM_{197} protein. The polysaccharides are produced from fermentation and purification of *Neisseria meningitidis* (serogroups A, C, W-135 or Y). MenA, MenW-135 and MenY polysaccharides are purified by several extraction and precipitation steps. MenC polysaccharide is purified by a combination of chromatography and precipitation steps. The protein carrier (CRM_{197}) is produced by bacterial fermentation and is purified by a series of chromatography and ultrafiltration steps.

The oligosaccharides are prepared by hydrolysis, sizing, activation and conjugation. Each oligosaccharide is covalently linked to the CRM_{197}. The resulting glycoconjugates are purified to yield the four drug substances, which compose the final vaccine. No preservative or adjuvant is added during manufacturing. The vaccine contains no thiomersal.

3. PHARMACEUTICAL FORM

MENVEO is presented as meningococcal group A (MenA) lyophilised conjugate component and a meningococcal group C, W-135 and Y (MenCWY) liquid conjugate component.

The MenA conjugated component is a white to off-white powder for injection and MenCWY conjugated component is a colourless clear solution for injection.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

MENVEO is indicated for active immunisation of infants and children (from 2 months of age), adolescents and adults to prevent invasive disease caused by *Neisseria meningitidis* serogroups A, C, W135 and Y. The use of this vaccine should be in accordance with official recommendations.

4.2 DOSE AND METHOD OF ADMINISTRATION

<table>
<tr><th colspan="3">Children from 2 to 23 months of age</th><th rowspan="2">Children from 2 to 10 years of age</th><th rowspan="2">Adolescents (from 11 years of age) and adults</th></tr>
<tr><th colspan="2">Infants initiating vaccination from 2 to 6 months of age</th><th>Unvaccinated infants and toddlers greater than 6 to 23 months of age</th></tr>
<tr><th>3-dose schedule*≠</th><th>4-dose schedule</th><th>2-dose schedule</th><th>1 single dose</th><th>1 single dose</th></tr>
<tr><td>- 1st dose as from 2 months of age
- 2nd dose 2 months after 1st dose
- 3rd dose as early as possible during the second year of life</td><td>- 3 doses, with a minimum interval of 2 months between each dose
- 4th dose during the second year of life (at 12-16 months)</td><td>2 doses, with a minimum interval of 2 months.

The second dose is to be administered during the second year of life.</td><td></td><td></td></tr>
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* If optimal protection against serogroup A is required (for example, travellers to areas where serogroup A is endemic), a 4-dose schedule should be used (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS).

≠ Infants with medical conditions associated with increased risk of invasive meningococcal disease should receive a 4-dose schedule (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS).

These dosing recommendations should be reviewed in conjunction with the Australian Immunisation Handbook. The need for, and timing of, a booster dose of MENVEO has not yet been determined.

Preparation for Administration

MENVEO must be prepared for administration by reconstituting the lyophilised MenA conjugate component with the liquid MenCWY conjugate component.

Powder in vial and solution in pre-filled syringe:
Remove the tip cap from the syringe and attach a suitable needle for the withdrawal (21G 1½ inch length or 21G, 40 mm length). Use the whole contents of the syringe to reconstitute the MenA conjugate component in vial.

Powder in vial and solution in vial:
Using a syringe and suitable needle (21G, 1½ inch length or 21G, 40 mm length) withdraw the entire contents of the vial of solution and inject into the vial of powder to reconstitute the MenA conjugate component.

Invert and shake the vial vigorously and then withdraw 0.5 mL of reconstituted product. Please note that it is normal for a small amount of liquid to remain in the vial following withdrawal of the dose. Prior to injection, change the needle with one suitable for the administration. Ensure that no air bubbles are present in the syringe before injecting the vaccine.

Following reconstitution, the vaccine is a clear, colourless solution, free from visible foreign particles. In the event of any foreign particulate matter and/or variation of physical aspect being observed, discard the vaccine.

Method of administration

MENVEO should be administered as a single 0.5 mL intramuscular injection, preferably into the anterolateral aspect of the thigh in infants or into the deltoid muscle (upper arm) in children, adolescents and adults.

Do not administer MENVEO intravenously, subcutaneously or intradermally.

Separate injection sites must be used if more than one vaccine is being administered at the same time.

MENVEO must not be mixed with other vaccines in the same syringe or vial. Separate injection sites must be used if more than one vaccine is being administered at the same time.

MENVEO is for single use in one patient only.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients of the vaccine (see section 6.1 List of Excipients), including diphtheria toxoid (CRM_{197});
- Known hypersensitivity to other diphtheria-containing vaccines;
- Known hypersensitivity to latex. The tip cap of the syringe contains 10% Dry Natural Rubber. Dry Natural Rubber is considered to present a much lower risk of allergy compared with natural rubber latex. Notwithstanding this, the healthcare professional is encouraged to consider the benefit: risk prior to administering this vaccine to patients with known history of hypersensitivity to latex.
- Acute febrile illness of any cause;
- A life-threatening reaction after previous administration of a vaccine containing similar components is a contraindication to vaccine administration.

4.4 SPECIAL WARNINGS AND PRECAUTIONS

MENVEO has not been evaluated in persons with thrombocytopenia or bleeding disorders. Because of the risk of hematoma, MENVEO should not be administered to persons with any bleeding disorder, such as haemophilia or thrombocytopenia, or to persons receiving anticoagulant therapy, unless the potential benefit outweighs the risk of administration. When intramuscular vaccine is indicated for a patient with a bleeding disorder or a person receiving anticoagulant therapy, the vaccine should be administered intramuscularly if, in the opinion of a physician familiar with the patient's bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives anti-haemophilia or similar therapy, intramuscular vaccinations can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or finer) should be used for the vaccination and firm pressure applied to the site, without rubbing, for 2 minutes or more. The patient or family should be instructed concerning the risk of hematoma from the injection.

Appropriate precautions should be taken before administration of MENVEO to minimise the risk of adverse reactions. These precautions include reviewing the subject’s immunisation and medical history for the presence of any contraindications to immunisation, such as possible hypersensitivity to MENVEO or similar vaccines (including diphtheria-containing vaccines) and evaluating the patient’s current health status.

As with all injectable vaccines, as a precautionary measure, adrenaline injection (1:1000), other appropriate agents and equipment, and appropriate medical treatment

and supervision must always be immediately available in case of a rare anaphylactic event or serious allergic reactions following administration of the vaccine.

As with other vaccines, vaccination with MENVEO should be postponed in individuals suffering from an acute severe febrile illness (see section 4.3 Contraindications). The presence of a minor infection is not contraindicated.

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection (see section 4.8 Adverse Effects). It is important that procedures are in place to avoid injury from fainting.

As for all vaccines, the date of vaccine administration, the lot number and the manufacturer of the vaccine administered should be recorded in the patient's immunisation record.

Do not administer the vaccine intravascularly, subcutaneously or intradermally.

Care should be taken to avoid injecting MENVEO vaccine subcutaneously, since clinical studies have not been conducted to establish the vaccine’s safety and immunogenicity when administered subcutaneously.

A separate sterile syringe and needle should be used for each patient to prevent transmission of blood-borne infectious agents from person to person. Needles should not be recapped and should be disposed of according to guidelines for management of biohazardous waste.

The four dose schedule should be considered for infants travelling internationally to areas where serogroup A is endemic, see section 5.2 PHARMACODYNAMIC PROPERTIES.

MENVEO is not indicated to prevent invasive meningococcal disease caused by serogroup B or other serogroups of *N. meningitidis* not present in the vaccine, nor to prevent infections caused by other microorganisms.

MENVEO is not indicated for treatment of meningococcal disease.

There are no data on the applicability of the vaccine for post-exposure prophylaxis.

As with any vaccine, a protective immune response may not be elicited in all vaccinees (see section 5.1 Pharmacodynamic Properties - Clinical Trials).

In immunocompromised individuals, vaccination may not result in an appropriate protective antibody response. MENVEO has not been evaluated in the immunocompromised, including individuals with HIV infection, complement deficiencies and individuals with functional or anatomical asplenia may not mount an immune response to meningococcal group A, C, W-135 and Y conjugate vaccines.

A possible association between Guillain-Barré Syndrome (GBS) and receipt of the US and Canadian licensed quadrivalent diphtheria toxoid conjugate A, C, W-135 and Y vaccine (Menactra®, Sanofi Pasteur) was reported in 2005. At present, it is unclear if this represents a true or a fortuitous association. The US Centres for Disease Control and Prevention (CDC) conducted an analysis of the 17 cases of GBS occurring among Menactra recipients and concluded that the relative risk for GBS post Menactra, relative to the background risk in the general population, was 1.78 (95% CI 1.02-2.85). Since the background rate of GBS is very low (0.1/100,000 person months) and the disease is generally self-limited with a low case fatality rate in this population, this equates to an extremely small burden of attributable disease impact. In subsequent analysis, when factoring in the prevention of meningococcal disease, and thus the overall risk/benefit balance, the CDC concluded that vaccination was clearly beneficial, with vaccination saving 2400 Quality Adjusted Life Years (QALYs) due to prevention of meningococcal disease, at a cost of 5 QALYs due to vaccine induced GBS (Cho, 2010). On this basis, vaccination was judged to be the preferred strategy and for this reason, the recommendation for routine use of Menactra in adolescents continues. The decision to administer MENVEO to subjects with a known history of Guillain-Barré Syndrome should take into account the potential benefits and risks.

Individuals receiving treatment that inhibits terminal complement activation (for example, eculizumab) remain at increased risk of invasive disease caused by Neisseria meningitidis groups A, C, W-135 and Y even following vaccination with MENVEO.

Paediatric use

Safety and immunogenicity of MENVEO in children under 2 months of age have not been established.

Use in the elderly

Limited data are available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

MENVEO must not be mixed with other vaccines in the same syringe or vial. Concomitant vaccines should always be administered at separate and preferably contralateral sites.

If a vaccine recipient is undergoing immunosuppressant treatment, the immunological response may be diminished.

Children from 2 to 23 months of age
MENVEO can be given concomitantly with any of the following monovalent or combination vaccines: diphtheria, acellular pertussis, tetanus, *Haemophilus influenzae* type b (Hib), inactivated polio, hepatitis B (HBV), inactivated hepatitis A, 7-valent and 13-valent pneumococcal conjugate vaccine (PCV7 and PCV13), pentavalent rotavirus, and measles, mumps, rubella and varicella (MMRV). No increase in the reactogenicity or change in the safety profile of the routine vaccines was observed in clinical trials.

No immune interference was observed for the concomitantly administered vaccines with exception of pneumococcal vaccine serotype 6B and 19A in one study, and against pneumococcal vaccine serotype 19A in another study, both post-dose 3. No immune interference was observed post-dose 4 for any pneumococcal vaccine serotypes.

Children from 2 to 10 years of age
The safety and immunogenicity of other childhood vaccines when administered concomitantly with MENVEO have not been evaluated.

Adolescents from 11 to 18 years of age
MENVEO can be given concomitantly with any of the following monovalent or combination vaccines: tetanus, reduced diphtheria and acellular pertussis vaccine (dTpa)) and human papillomavirus quadrivalent (Types 6, 11, 16 and 18) recombinant vaccine (HPV). There was no evidence of increased reactogenicity, change in safety profile, or impact on the antibody response of the vaccines following co-administration in clinical trials.

The sequential administration of MENVEO one month after dTpa resulted in lower immune response for serogroup W-135 as measured by subjects with sero response. The clinical relevance of this observation is however unknown.

Adults
MENVEO can be given concomitantly with any of the following monovalent or combination vaccines: hepatitis A and B, yellow fever, typhoid fever (V1 polysaccharide), Japanese encephalitis and rabies. No change in the safety profile of the vaccines was observed when co-administered with MENVEO in clinical trials and no clinically relevant interference was shown in the antibody response to the vaccines.

Concomitant administration of MENVEO and other vaccines than those listed above has not been studied. If MENVEO is given at the same time as another injectable vaccine, the vaccine should always be administered at a difference injection site.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

There were no effects on mating performance or fertility of female rabbits receiving the clinical dose of MENVEO three times pre-mating and twice during gestation. Each dose was approximately 15-fold higher than the human dose on body weight basis.
Impairment of male fertility in rabbits was not evaluated.

Use in Pregnancy

(Category B1)
Insufficient clinical data on exposed pregnancies are available.
No information is available on administration of MENVEO to pregnant women.
MENVEO vaccine should be given to pregnant women following assessment of the risk and benefit.

In a study in rabbits immunised with MENVEO three times prior to mating, and on gestation days 7 and 20, there were no treatment-related effects on pregnancy, foetuses, or kits. Antibodies to the vaccine were detected in vaccine-treated dams, foetuses, and kits.

Use in Lactation

It is not known whether MENVEO is secreted in human milk. However, as with other polysaccharide vaccines, it is unlikely that secreted antibodies in milk would be harmful

when ingested by a breastfed infant. MENVEO should only be administered to women who are breastfeeding when needed and the possible advantages outweigh the possible risks.

MENVEO administration to maternal animals prior to mating and during gestation had no effects on development of offspring, assessed to lactation day 29. The vaccine was immunogenic in maternal animals and antibodies were detected in the offspring, but antibodies levels in milk were not determined.

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. Dizziness has been very rarely reported following vaccination. This may temporarily affect the ability to drive or use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Children 2 to 23 months of age

Four dose infant series

The safety of MENVEO with 4-dose schedule was evaluated in three randomised, controlled multicenter clinical studies in which 8735 infants 2 months of age at enrolment received MENVEO concomitantly with routine paediatric vaccines (see Interactions with Other Medicines). A total of 2864 infants received the routine paediatric vaccines alone.

The reported frequencies of solicited local and systemic adverse reactions in the largest multinational MENVEO safety study are presented in Table 1.

Table 1: Study V59P23: Rates of solicited adverse reactions reported in children 2 months of age and older, during the 7 days following each vaccination with MENVEO administered with routine childhood vaccines, or routine childhood vaccines alone, at 2, 4, 6 and 12 months of age[a]

	Dose 1		Dose 2		Dose 3		Dose 4	
	MENVEO with Routine[b] %	**Routine Vaccines[b]** %	**MENVEO with Routine[b]** %	**Routine Vaccines[b]** %	**MENVEO with Routine[b]** %	**Routine Vaccines [b]**%	**MENVEO with Routine[b]** %	**Routine Vaccines[b]** %
Local Adverse Reactions[c]	N= 1250-1252	N= 428	N= 1205-1207	N= 399	N= 1056-1058	N= 351-352	N= 1054-1055	N= 334-337
Tenderness, any	41	45	31	36	24	32	29	39
Tenderness, severe[d]	3	5	2	2	1	3	1	1
Erythema, any	11	14	12	21	14	23	15	25
Erythema, >50 mm	<1	<1	0	0	0	0	0	0
Induration, any	8	16	9	17	8	19	8	21
Induration, >50 mm	0	<1	0	0	0	0	0	0
Systemic Adverse Reactions	N= 1246-1251	N= 427-428	N= 1119-1202	N= 396-398	N= 1050-1057	N= 349-350	N= 1054-1056	N= 333-337
Irritability, any	57	59	48	46	42	38	43	42
Irritability, severe [e]	2	2	1	3	1	1	2	1
Sleepiness, any	50	50	37	36	30	30	29	27
Sleepiness, severe [f]	2	1	1	1	<1	<1	1	0
Persistent crying, any	41	38	28	24	22	17	21	18
Persistent crying, ≥ 3 hours	2	2	2	2	1	1	1	1
Change in eating habits, any	23	24	18	17	17	13	19	16
Change in eating habits, severe [g]	1	1	1	1	1	<1	1	0
Vomiting, any	11	9	7	6	6	4	5	4
Vomiting, severe [h]	<1	0	<1	0	<1	0	<1	0
Diarrhea, any	16	11	11	8	8	6	13	9
Diarrhea, severe [i]	<1	<1	<1	<1	1	<1	1	1
Rash [j]	3	3	3	4	3	3	4	3
Fever ≥38.°C [k]	3	2	4	6	7	6	9	7
Fever 38.0-38.9°C	3	2	4	5	7	6	6	5
Fever 39.0-39.9°C	0	0	1	1	<1	0	2	2
Fever ≥40.0°C	0	<1	0	<1	0	0	<1	0

N= number of subjects who completed the diary card for a given symptom at the specified vaccination.

[a] As Treated Safety Sub-population = US children who received at least one dose of study vaccine and whose diary cards were completed per protocol and returned to the site.

[b] Routine childhood vaccines include DTaP-IPV-Hib and PCV7 at doses 1,2,3 and PCV7, MMRV and Hepatitis A vaccines at dose 4. HBV and rotavirus vaccines were allowed according to Prescribing Information.

[c] Local reactogenicity of Menveo and PCV7 was assessed.

[d] Tenderness, severe = cried when injected limb moved.

[e] Irritability, severe = unable to console.

[f] Sleepiness, severe = sleeps most of the time, hard to arouse.

[g] Change in eating habits, severe = missed > 2 feeds.

[h] Vomiting, severe = little/no intake for more prolonged time.

[i] Diarrhea, severe = ≥ 6 liquid stools, no solid consistency.

[j] Rash was assessed only as present or not present, without a grading for severity

[k] Axillary temperature.

Three dose infant series

The safety of MENVEO was assessed in 476 infants who completed a 3-dose infant series, including 297 who received doses at 2,6 and 12 months and 179 who received doses are 2,4 and 12 months of age.

The reported frequencies of solicited local and systemic adverse reactions in study V59_36 for the 3-dose and 4-dose infant series were comparable.

Two dose primary series

The safety of MENVEO with 2-dose schedule was assessed in 1985 children immunised between 6 and 23 months of age, in three randomised studies that addressed the safety of MENVEO administered concomitantly with routine paediatric vaccines.
In two studies, the safety of one dose of MENVEO when given concomitantly with routine paediatric vaccines in the second year of life was evaluated in 345 subjects. Most of the common adverse reactions occurred within the first several days after vaccination and few were severe.

Table 2 lists the solicited adverse reactions following MENVEO administered alone at 7- 9 months and concomitantly with MMRV at 12 months in a randomized, controlled, multicenter study conducted in the U.S (V59P21). The rates of solicited adverse reactions reported were comparable between the concomitantly administered group (MENVEO with MMRV) and the group which received MMRV alone, or MENVEO alone. The frequency and severity of solicited local and systemic reactions occurring within 7 days following vaccination at 12 months of age, are shown in Table 2.

Table 2: Study V59P21: Rates of solicited adverse reactions reported in children during the 7- days following vaccination with MENVEO administered at 7-9 months and 12 months of age, MENVEO administered alone at 7-9 months and with MMRV at 12 months of age, and MMRV administered alone at 12 months of age[a]

	MENVEO Group		MENVEO + MMRV Group		MMRV Group
	MENVEO 7-9 months %	**MENVEO 12 months %**	**MENVEO 7-9 months %**	**MENVEO with MMRV 12 months**	**MMRV 12 months %**
Local Adverse Reactions– MENVEO site	N=460-462	N=381-384	N=430-434	N= 386-387	
Tenderness, any	11	10	11	16	N/A
Tenderness, severe [b]	<1	<1	<1	0	N/A
Erythema, any	15	13	13	12	N/A
Erythema, >50 mm	<1	<1	0	1	N/A
Induration, any	8	8	7	8	N/A
Induration, >50 mm	<1	<1	0	1	N/A
Local Adverse Reactions– MMRV site				N=382-383	N=518-520
Tenderness, any	N/A	N/A	N/A	16	19
Tenderness, severe [b]	N/A	N/A	N/A	0	<1
Erythema, any	N/A	N/A	N/A	15	14
Erythema, >50 mm	N/A	N/A	N/A	1	<1
Induration, any	N/A	N/A	N/A	13	8
Induration, >50 mm	N/A	N/A	N/A	<1	0
Systemic Adverse Reactions	N=461-463	N=385-386	N=430-434	N=387-389	N=522-524
Irritability, any	40	27	37	37	44
Irritability, severe [c]	2	2	2	1	3
Sleepiness, any	26	17	29	26	32
Sleepiness, severe [d]	2	1	1	1	2
Persistent crying, any	21	12	20	19	20
Persistent crying, ≥ 3 hours	2	1	1	1	2
Change in eating habits, any	17	12	17	20	20
Change in eating habits, severe [e]	<1	1	1	2	1
Vomiting, any	9	6	9	6	6
Vomiting, severe [f]	<1	<1	<1	<1	<1
Diarrhea, any	16	10	15	15	20
Diarrhea, severe [g]	2	1	<1	1	2
Rash [h]	3	5	6	6	8
Fever ≥38.0°C [i]	5	5	6	9	7
Fever 38.0-38.9°C	3	3	5	7	7
Fever 39.0-39.9°C	2	2	1	1	1
Fever ≥40.0°C	<1	1	<1	<1	0

	MENVEO Group		MENVEO + MMRV Group		MMRV Group
	MENVEO 7-9 months %	**MENVEO 12 months %**	**MENVEO 7-9 months %**	**MENVEO with MMRV 12 months**	**MMRV 12 months %**

number of subjects who completed the diary card for a given symptom at the specified vaccination.
[a] As Treated Safety Sub-population = Children who received at least one dose of study vaccine and whose diary cards were completed per protocol and returned to the site.
[b] Tenderness, severe = cried when injected limb moved.
[c] Irritability, severe = unable to console.
[d] Sleepiness, severe = sleeps most of the time, hard to arouse.
[e] Change in eating habits, severe = missed > 2 feeds.
[f] Vomiting, severe = little/no intake for more prolonged time.
[g] Diarrhea, severe = $\geq$ 6 liquid stools, no solid consistency.
[h] Rash was assessed only as present or not present, without a grading for severity
[i] Axillary temperature.

Serious Adverse Events

Serious adverse events in subjects receiving a four-dose series of MENVEO at 2, 4, 6 and 12-16 months were evaluated in three randomized multicenter clinical studies. In the two controlled studies, the proportions of infants randomized to receive the four-dose MENVEO series concomitantly with routine vaccinations and infants who received routine vaccinations alone that reported serious adverse events during different study periods were, respectively: a) 2.7% and 2.2%, during the infant series; b) 2.5% and 2.5%, between the infant series and the fourth dose; c) 0.3% and 0.3%, in the one month following the fourth dose; and d) 1.6% and 2.2%, during the 6 months follow up period after the last dose. In the third study, which was controlled up to the fourth dose, the proportions of infants randomized to dosing regimens that included receiving four doses of MENVEO concomitantly with routine vaccinations at 2, 4, 6, and 12-16 months and infants who received routine vaccinations alone that reported serious adverse events during different study periods were, respectively: a) 3.5% and 3.6%, during the infant series; and b) 2.8% and 3.3%, between the infant series and the 12-16 dose; and c) 0.5% and 0.7%, in the one month following the fourth dose. In the same study, 1.9% of infants randomized to receive the four-dose MENVEO series concomitantly with routine vaccinations reported serious adverse events during the 6 month follow up period after the fourth dose. The most common serious adverse events reported in these three studies were wheezing, pneumonia, gastroenteritis and convulsions, and most occurred at highest frequency after the infant series.

In a study of children aged 7-23 months randomized to receive the two-dose MENVEO series concomitantly with MMRV at 12 months of age, the rates of serious adverse events during the study, including the 6-month follow-up period after the last dose, were 3.6% and 3.8%, for the MENVEO with MMRV and MENVEO-only groups, respectively. Infants receiving MMRV alone, who had a shorter period of study

participation as they were enrolled at 12 months of age, had a lower rate of serious adverse events (1.5%). Among 1597 study subjects, included in the safety population, the most commonly reported serious adverse events in all study arms combined were dehydration (0.4%) and gastroenteritis (0.3%).

Across the submitted studies of individuals 2 through 23 months of age, within 28 days of vaccination, two deaths were reported in the MENVEO treatment groups (one case of sudden death and one case of sepsis), while no deaths were reported in the control group. None of the deaths was assessed as related to vaccination.

Among subjects with symptom onset within 42 days of vaccination (days 12, 25, 29), 3/12049 [0.02%, 95% CI: (0.01%,0.07%)] MENVEO recipients and 0/2877 [0%, 95% CI: (0%, 0.13%)] control recipients were diagnosed with Kawasaki Disease. One case of acute disseminated encephalomyelitis with symptom onset 29 days post-dose 4 was observed in a participant given MENVEO co-administered with routine US childhood vaccines at 12 months of age (including MMR and varicella vaccines).

Children 2 to10 years of age

The characterisation of the safety profile of MENVEO in children 2 to 10 years of age is based on data from 4 clinical trials in which 3181 subjects received MENVEO. Table 3 shows the solicited reactions from the pivotal study comparing MENVEO to Menactra (V59P20) in children 2 to 10 years of age.

Table 3: Study V59P20: Rates of solicited adverse reactions within 7-days following a single vaccination in children 2 years through 5 years and 6 years through 10 years of age.

Participants 2 to 5 Years of Age			
		MENVEO N =693 N(%)	**Menactra N = 684 N (%)**
Local			
Pain[§]	Any	226 (33)	241 (35)
	Severe	6 (1)	3 (<1)
Erythema [¥]	Any	186 (27)	170 (25)
	Severe	5 (1)	2 (<1)
Induration [¥]	Any	126 (18)	126 (18)
	Severe	3 (<1)	2 (<1)
Systemic ‡			
Irritability[§]	Any	147 (21)	152 (22)
	Severe	6 (1)	9 (1)
Sleepiness[§]	Any	109 (16)	126 (18)
	Severe	6 (1)	4 (1)

Change in Eating Habits[§]	Any	64 (9)	69 (10)
	Severe	4 (1)	2 (<1)
Diarrhea[§]	Any	50 (7)	53 (8)
	Severe	1 (<1)	0
Headache[§]	Any	33 (5)	39 (6)
	Severe	0	2 (<1)
Rash[*]	Any	30 (4)	34 (5)
Vomiting[§]	Any	21 (3)	21 (3)
	Severe	1 (<1)	0
Arthralgia[§]	Any	24 (3)	24 (4)
	Severe	1 (<1)	0
Fever[†]	Any	15 (2)	17 (2)
	Severe	0	0
Participants 6 through 10 Years of Age			
		MENVEO N = 582 N (%)	**Menactra N = 571 N (%)**
Local			
Injection site pain[§]	Any	226 (39)	256 (45)
	Severe	3 (1)	9 (2)
Erythema[¥]	Any	164 (28)	126 (22)
	Severe	7 (1)	1 (<1)
Induration[¥]	Any	97 (17)	73 (13)
	Severe	2 (<1)	0
Systemic ‡			
Headache[§]	Any	103 (18)	77 (13)
	Severe	5 (1)	7 (1)
Malaise[§]	Any	82 (14)	62 (11)
	Severe	8 (1)	7 (1)
Myalgia[§]	Any	61 (10)	59 (10)
	Severe	4 (1)	5 (1)
Nausea[§]	Any	49 (8)	37 (6)
	Severe	4 (1)	2 (<1)
Arthralgia[§]	Any	37 (6)	25 (4)
	Severe	0	2 (<1)
Chills[§]	Any	30 (5)	26 (5)
	Severe	0	2 (<1)
Rash*	Any	28 (5)	19 (3)
Fever[†]	Any	13 (2)	10 (2)
	Severe	0	2 (<1)

§ Severe: Unable to perform normal daily activity.
¥ Severe: ≥ 100mm.
* Rash was assessed only as present or not present, without a grading for severity.
† Any: ≥ 38°C, Severe: ≥ 40°C. Parents reported the use of antipyretic medication to treat or prevent symptoms in 11% and 13% of subjects 2 through 5 years of age, 9% and 10% of subjects 6 through 10 years of age for Menveo and Menactra, respectively.
‡ Different systemic reactions were solicited in different age groups

Serious Adverse Events

The information regarding serious adverse events in subjects aged 2 to 10 years was

derived from 3 randomized, controlled clinical trials, in which subjects received MENVEO, Menomune or Menactra. A fourth supportive trial provided serious adverse event information for subjects after one or two doses of MENVEO. Safety follow-up ranged from 6 to 12 months and included 2883 subjects administered MENVEO.

Serious adverse events reported during the safety follow-up periods occurred in 21/2883 (0.7%) of MENVEO subjects, in 7/1255 (0.6%) of Menactra subjects, and 2/861 (0.2%) of Menomune subjects. In the subjects receiving either one or two doses of MENVEO, there were 6 subjects with pneumonia, 3 subjects with appendicitis, and 2 subjects with dehydration; all other events were reported for only one subject. Among 1255 subjects receiving a single dose of Menactra and the 861 subjects receiving Menomune, there were no events reported by more than one subject.

The serious adverse events occurring within the first 30 days of vaccination were as follows: MENVEO (6/2883 [0.2%]) – appendicitis, pneumonia, staphylococcal infection, dehydration, febrile convulsion, and tonic convulsion; Menactra (1/1255 [0.1%]) – inguinal hernia; Menomune (2/861 [0.2%]) – abdominal pain, lobar pneumonia. In an additional 4th supportive study, 298 subjects received one or two doses of MENVEO and 22 (7%) had serious adverse events over a 13-month follow-up period including 13 subjects with varicella and 2 subjects with laryngitis. All other events were reported to occur in one subject. During the 30 days post vaccination in this study, one limb injury and one case of varicella were reported.

Adolescents and adults from 11 to 65 years of age

The safety of MENVEO was evaluated in 5 randomised controlled clinical trials including 6724 participants (from 11 years of age through adulthood) who received MENVEO and 1966 who received a comparator vaccine (either Menomune or Menactra). Demographic characteristics of subjects who received MENVEO were similar to those who received the comparator vaccine.

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

Frequencies are defined as follows:
Very common: (≥ 1/10)
Common: (≥1/100 to <1/10)
Uncommon: (≥1/1,000 to <1/100)
Rare: (≥1/10,000 to <1/1,000)
Very rare: (<1/10,000)

Not known: (cannot be estimated from the available data)

Infections and infestations:
Uncommon: nasopharyngitis

Nervous system disorders:
Very common: headache
Uncommon: dizziness

Gastrointestinal disorders:
Very common: nausea

Skin and subcutaneous tissue disorders:
Common: rash

Musculoskeletal and connective tissue disorders:
Very common: myalgia
Common: arthralgia

General disorders and administration site conditions:
Very common: injection site pain, injection site erythema (≤ 50 mm), injection site induration (≤ 50 mm), malaise
Common: injection site erythema (> 50 mm), injection site induration (> 50 mm), fever ≥ 38°C, chills
Uncommon: injection site pruritus

Post-marketing Observational Safety Study

In a post-marketing observational safety study conducted in a United States health maintenance organization, data from electronic health records of 48899 persons 11 through 21 years of age were used to evaluate pre-specified events of interest following vaccination with MENVEO. Using a self-controlled case series method, Bell's palsy showed a statistically significant increased risk in the period 1 to 84 days post-vaccination compared to the control period, with an overall adjusted relative incidence of 2.9 (95% CI: 1.1-7.5). Among the 8 reported cases of Bell's palsy, 6 cases occurred in persons who received MENVEO concomitantly with one or more of the following vaccines: dTpa, HPV, and Influenza vaccine. All reported Bell's palsy cases resolved.

Adverse reactions from post-marketing spontaneous reports

Because these events were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish, for all events, a causal relationship to vaccine exposure.

Blood and lymphatic system disorders:
Local lymphadenopathy.

Immune system disorders:
Hypersensitivity including anaphylaxis.

Nervous system disorders:
Dizziness, syncope, tonic convulsion, febrile convulsion, headache, facial paresis, balance disorder.

Eye disorders:
Eyelid ptosis.

Ear and labyrinth disorders:
Hearing impaired, ear pain, vertigo, vestibular disorder.

Respiratory, thoracic and mediastinal disorders:
Oropharyngeal pain.

Skin and subcutaneous tissue disorders:
Bullous conditions.

Musculoskeletal and connective tissue disorders:
Arthralgia, bone pain.

General disorders and administration site conditions:
Injection site pruritus, pain, erythema, inflammation and swelling, including extensive swelling of the injected limb, fatigue, malaise, pyrexia.

Investigations:
Alanine aminotransferase increased, body temperature increased

Injury, poisoning and procedural complications:
Fall, head injury.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSAGE

Insufficient data are available.

For information on management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Meningococcal vaccines, ATC code: JO7AH08.

Mechanism of Action

Meningococcal disease is caused by a gram-negative diplococcus, *Neisseria meningitidis*. *N. meningitidis* causes life-threatening disease worldwide. Based on antigenic variations in capsular polysaccharide structure, 13 serogroups of *N. meningitidis* have been identified.

Globally, 5 serogroups, A, B, C, W-135 and Y, cause almost all invasive meningococcal infections. Invasive infection by *N. meningitidis* most often manifests as bacteraemia and/or meningitis and can also more rarely present as arthritis, myocarditis, pericarditis, endophthalmitis, pneumonia or infection at other anatomic sites.

Early clinical manifestations of meningococcal disease are often nonspecific and may initially be difficult to distinguish from less serious illnesses. Symptoms may include headache, stiff neck, fever, chills, malaise and prostration. Disease can progress rapidly, with most cases seeking medical attention within 24 hours of symptom onset. About 10% of cases die, even with appropriate antimicrobial and supportive treatment; with meningococcal septicaemia up to 40% of cases die (Rosenstein, 1999). Permanent sequelae, including scarring, limb or digit loss, neurologic dysfunction, and/or hearing loss occur in 11–19% of survivors (Erickson, 1998).

Asymptomatic colonization of the upper respiratory tract by encapsulated *N. meningitidis* is common. Transmission is thought to occur by droplet transmission of respiratory tract secretions. Only a small percentage of colonised individuals develop disease.

The incidence of meningococcal disease is highest in children less than 5 years old, with infants under 12 months old at the greatest risk. Another incidence peak occurs in adolescents.

Bactericidal anti-capsular antibodies protect against invasive meningococcal disease. Vaccination with MENVEO leads to the production of bactericidal antibodies directed against the capsular polysaccharides of serogroups A, C, W-135 and Y. The original correlate of protection against meningococcal disease was a bactericidal activity (using human serum as the complement source (hSBA)) of ≥1:4 (Goldschneider, J. Exp Med, 1969); an hSBA ≥1:8 is a more conservative correlate of protection.

Clinical Trials

The immunogenicity of MENVEO was evaluated in randomised, multicenter, active controlled clinical trials that enrolled persons from 2 months through 65 years of age.

The primary serologic endpoint for many of the clinical trials was subject serological response. This was defined as a post vaccination titre of ≥1:8 for subjects who were seronegative at baseline, or a fourfold rise for subjects who were seropositive at baseline. Other endpoints included the proportion of subjects who had post vaccination titres of ≥1:8 or ≥1:4 and geometric mean titres (GMTs).

Correlate of Protection Due to the infrequency of clinical disease, the efficacy of MENVEO is inferred from the results of a functional assay. The primary measure of immune response and protection was induction of serogroup-specific anti-capsular antibodies with bactericidal activity. Serum bactericidal activity (SBA) was measured using human serum as the source of exogenous complement (hSBA). The hSBA was the original correlate of protection against meningococcal disease (Goldschneider I., et al, 1969 a, b).

Immune responses following a 4-dose infant series (2 months through 16 months of age)

The pre-specified endpoint for immunogenicity of MENVEO in infants receiving a 4-dose series at 2, 4, 6 and 12 months of age was the proportion of subjects achieving an hSBA ≥ 1:8, with the lower limit of the 2-sided 95% Confidence Intervals (CI) for the point estimate being ≥ 80% of vaccinees for serogroup A, and ≥ 85% of vaccinees for

serogroups C, W-135 and Y one month following the final dose. Sera were obtained at 2 months (prior to the first infant dose), at 7 months (1 month after the infant series), 12 months (prior to the older infant dose), and 13 months of age (1 month after the final dose) which allowed evaluation of the immunogenicity of the infant series as well as of the complete series.

The immunogenicity of MENVEO in infants was assessed in two pivotal randomised, controlled, multicentre studies of infants, who received a 4-dose series at 2, 4, 6 and 12 months of age and subjects who received a 4-dose series at 2, 4, 6, and 16 months of age. The pre-defined criteria for immunogenicity were met for all four serogroups A, C, W-135 and Y at one month following completion of a 4-dose series at 2, 4, 6 and 12 - 16 months (Table 4).

Table 4: Bactericidal antibody responses following administration of MENVEO with routine paediatric vaccines at 2, 4, 6 and 12 or 16 months of age.

		2, 4, 6, 12 months of age				**2, 4, 6, 16 months of age**	
Serogroup		**Study V59P14 – US subjects**		**Study V59_33**		**Study V59P14 – Latin America subjects**	
		Post 3rd dose	**Post 4th dose**	**Post 3rd dose**	**Post 4th dose**	**Post 3rd dose**	**Post 4th dose**
A		N = 212	N = 84	N=202	N=168	N=268	N=120
	% ≥1:8 95% CI	67 (61, 74)	94 (87*, 98)	76 (69, 81)	89 (83*, 93)	89 (85, 93)	95 (89, 98)
	GMT 95% CI	13 (11, 16)	77 (55, 109)	21 (17, 26)	54 (44, 67)	43 (36, 52)	146 (113, 188)
C		N = 204	N = 86	N=199	N=156	N=272	N=122
	% ≥1:8 95% CI	97 (93, 99)	98 (92*, 100)	94 (90, 97)	95 (90*, 98)	97 (94, 99)	98 (94, 100)
	GMT 95% CI	108 (92, 127)	227 155, 332)	74 (62, 87)	135 (107, 171)	150 (127, 177)	283 (225, 355)
W-135		N = 197	N = 85	N=194	N=153	N=264	N=112
	% ≥1:8 95% CI	96 (93, 99)	100 (96*, 100)	98 (95, 99)	97 (93*, 99)	98 (96,100)	100 (97, 100)
	GMT 95% CI	100 (86, 116)	416 (288, 602)	79 (67, 92)	215 (167, 227)	182 (159, 208)	727 (586, 903)
Y		N = 182	N = 84	N=188	N=153	N=263	N=109
	% ≥1:8 95% CI	96 (92, 98)	100 (96*, 100)	94 (89, 97)	96 (92*, 99)	98 (96, 99)	99 (95, 100)
	GMT 95% CI	73 (62, 86)	395 (269, 580)	51 (43, 61)	185 (148, 233)	125 (107, 146)	590 (463, 751)

* Prespecified criteria for adequacy of immune response were met (Study V59P14, US cohort: lower limit (LL) of 95% CI) ≥ 80% for serogroup A and ≥ 85% for serogroups C, W-135, and Y; Study V59_33: LL of the 95% CI > 80% for serogroup A and > 85% for serogroups C, W, and Y).
Serum Bactericidal Assay with exogenous human complement source (hSBA).
%≥1:8 = proportions of subjects with hSBA ≥ 1:8 against a given serogroup; CI = confidence interval; GMT = geometric mean antibody titre; N = number of infants eligible for inclusion in the Per-Protocol Immunogenicity population for whom serological results were available for the post-dose 3 and post-dose 4 evaluations.

Immune responses following a 3-dose infant series (2 months through 12 months of age)

In study V59_36, children 2 months of age at enrolment were administered either 4 doses at 2, 4, 6 and 12 months of age or 3 doses at 2, 4 and 12 months of age. By one month after the second vaccination (5 months of age), substantial increases in immune responses were seen for all 4 serogroups. The 3-dose series was shown to be non-inferior to the 4-dose series for serogroups C, W-135 and Y at 1 month after the 12 month vaccination. The hSBA GMTs at 13 months were also similar between the 3-dose and 4-dose groups for serogroups C, W-135 and Y (Table 5). Although immune responses to serogroup A were not included in the non-inferiority assessment, a relevant proportion of participants (88%) achieved seroprotective (hSBA titre ≥1:8) titre one month following the 3-dose primary schedule. Long term antibody persistence was not measured in this study.

Table 5: hSBA Geometric Mean Titres (95%CI) and the between-group ratios following a 3-dose series (2,4 and 12 months) and a 4-dose infant series of MENVEO with routine paediatric vaccines in study V59_36.

Serogroup	Menveo 3-dose 13 months		Menveo 4-dose 13 months		Menveo 3-dose: Menveo 4-dose
	N	GMT (95%CI)	N	GMT (95%CI)	GMT Ratio (95%CI)
A	146	59 (45, 77)	141	94 (76, 117)	0.63 (0.48, 0.84)
C	160	124 (99, 156)	152	160 (130, 198)	0.78 (0.6, 1.01)
W-135	153	248 (202, 303)	138	244 (195, 305)	1.02 (0.79, 1.31)
Y	154	212 (175, 258)	146	254 (203, 318)	0.84 (0.65, 1.07)

hSBA = Serum Bactericidal Assay with exogenous human complement source;

GMT = geometric mean antibody titre; CI = confidence interval; N = number of subjects analysed

Table 6: Percentages of subjects (95%CI) with hSBA titres ≥1:8 and the between-group differences following a 3-dose series (2,4 and 12 months) and a 4-dose infant series of MENVEO with routine paediatric vaccines in study V59_36.

Serogroup	Menveo 3-dose 13 months		Menveo 4-dose 13 months		Menveo 3-dose - Menveo 4-dose
	N	%≥1:8 (95%CI)	N	%≥1:8 (95%CI)	Group Difference (95%CI)
A	146	88 (82, 93)	141	96 (91, 98)	-7% (-14%, -1%)
C	160	95* (90, 98)	152	99 (95, 100)	-4% (-8%, 0%)
W-135	153	99* (96, 100)	138	99 (96, 100)	0% (-3%, 3%)
Y	154	100* (98, 100)	146	99 (96, 100)	1% (-2%, 4%)

hSBA = Serum Bactericidal Assay with exogenous human complement source;

CI = confidence interval; N = number of subjects analysed

* Non-inferiority criterion met (the lower limit of the two-sided 95% CI >-10 % for vaccine group differences [3-dose series minus 4-dose series]. Immune responses to serogroup A were not included in the non-inferiority criterion assessment.

In study V59P14, children 2 months of age at enrolment were administered either 3 doses at 2, 6 and 12 months of age or 4 doses at 2, 4, 6 and 18 months of age, and were assessed for immune response at 7 months of age. Among 284 infants who received doses at 2 and 6 months, 74%, 94%, 99%, 97% had hSBA ≥ 1:8 against serogroups A, C, W-135 and Y, respectively, compared to 89%, 97%, 98%, and 98% of 277 infants who received doses at 2, 4, and 6 months. Pre-specified non-inferiority criteria were met for serogroups C, W-135, and Y

Immune responses following a 2-dose series in children 7 months through 23 months of age

In study V59P21, the immunogenicity of MENVEO was assessed in children, who did not receive the 4-dose series but instead received a 2 dose series. Among the per protocol population of 386 subjects, after MENVEO administered at 7-9 and at 12 months, the proportions of subjects with hSBA ≥ 1:8 for serogroups A, C, W-135, and Y were respectively: 88% (84-91), 100% (98-100), 98% (96-100), 96% (93-99) (Table 7).

Table 7: Bactericidal antibody responses following administration of MENVEO at 7-9 and 12 months of age in study V59P21.

Serogroup		% hSBA≥1:8 (95%CI)	GMTs (95%CI)
Men A		N=379	N=379
	1 month post-first dose (8-10 months of age)	175 (50%) (45-56) N=349	8.16 (6.96-9.58) N=349
	1 month post-second dose (13 months of age)	334 (88%) (84-91)	37 (32-42)
Men C		N=199	N=199
	1 month post-first dose (8-10 months of age)	175 (88%) (83-92)	26 (22-31)
	1 month post-second dose (13 months of age)	195 (100%) (98-100) N=195	180 (158-205) N=195
Men W		N=199	N=199
	1 month post-first dose (8-10 months of age)	73 (37%) (30-44)	5.11 (4.15-6.29)
	1 month post-second dose (13 months of age)	193 (98%) (96-100) N=196	119 (101-139) N=196
Men Y		N=198	N=198
	1 month post-first dose (8-10 months of age)	60 (31%) (24-38) N=196	4.09 (3.36-4.98) N=196
	1 month post-second dose (13 months of age)	191 (96%) (93-99)	88 (73-105)

Serum Bactericidal Assay with exogenous human complement source (hSBA).
%≥1:8 = proportions of subjects with hSBA ≥ 1:8 against a given serogroup; CI = confidence interval; GMT = geometric mean antibody titre; N = number of infants eligible for inclusion in the Per-Protocol Immunogenicity population for whom serological results were available for the post-first dose and post-second dose evaluations.

A 2-dose series was also examined in a study of Latin American children, who received MENVEO at 12 and 16 months of age. Among the per protocol population of 106 subjects, the proportions of subjects with hSBA ≥1:8 for serogroups A, C, W-135 and Y were 97% (92-99), 100% (96-100), 100% (96-100), and 100% (96-100), respectively.

Immunogenicity in children (2-10 years of age)

In the pivotal study V59P20 immunogenicity of MENVEO was compared to Menactra® (Sanofi Pasteur); 1170 children were vaccinated with MENVEO and 1161 received the comparator vaccine in the per protocol populations.

In the pivotal, randomised, observer-blind study V59P20, in which participants were stratified by age (2 through 5 years and 6 through 10 years), the immunogenicity of a single dose of MENVEO one-month post vaccination was compared with the single dose of Menactra. In both age groups, non-inferiority of MENVEO to Menactra for the proportion of subjects with a seroresponse and percentage of subjects with hSBA ≥1:8 was demonstrated for serogroups C, W-135 and Y, but not for serogroup A. For both age groups (2-5 years and 6-10 years of age), the immune response as measured by hSBA GMTs was non-inferior for all serogroups (Table 8). In addition, the percentage of subjects with a seroresponse, percentage of subjects with hSBA ≥1:8, and GMT levels were statistically higher among MENVEO recipients for serogroups W-135 and Y. GMT levels were also statistically higher among MENVEO recipients for serogroup C.

Table 8: Comparison of serum bactericidal antibody responses to MENVEO and Menactra 1 month after vaccination of subjects 2 through 10 years of age.

	2-5 years			**6-10 years**			**2-10 years**		
Endpoint by Serogroup	**MENVEO (95% CI)**	**Menactra (95% CI)**	**Percent Difference (MENVEO – Menactra) or GMT ratio (MENVEO/ Menactra) (95% CI)**	**MENVEO (95% CI)**	**Menactra (95% CI)**	**Percent Difference (MENVEO – Menactra) or GMT ratio (MENVEO/ Menactra) (95% CI)**	**MENVEO (95% CI)**	**Menactra (95% CI)**	**Percent Difference (MENVEO – Menactra) or GMT ratio (MENVEO/ Menactra) (95% CI)**
A	N=606	N=611		N=551	N=541		N=1157	N=1152	
% Sero-response‡	72 (68, 75)	77 (73, 80)	-5 (-10.0, -0.3)	77 (73, 80)	83 (79, 86)	-6 (-11, -1)	74 (71,76)	80 (77,82)	-6* (-9, -2)
%≥1:8	72 (68, 75)	78 (74, 81)	-6 (-11, -1)	77 (74, 81)	83 (80, 86)	-6 (-11, -1)	75 (72, 77)	80 (78, 83)	-6* (-9,-3)
GMT	26 (22, 30)	25 (21, 29)	1.04* (0.86, 1.27)	35 (29, 42)	35 (29, 41)	1.01* (0.83, 1.24)	30 (27, 34)	29 (26, 33)	1.03* (0.89,1.18)
C	N=607	N=615		N=554	N=539		N=1161	N=1154	
% Sero-response‡	60 (56, 64)	56 (52, 60)	4 * (-2, 9)	63 (59, 67)	57 (53, 62)	6* (0, 11)	61 (58, 64)	57 (54, 60)	5* § (1, 9)
%≥1:8	68 (64, 72)	64 (60, 68)	4* (-1, 10)	77 (73, 80)	74 (70, 77)	3* (-2, 8)	72 (70, 75)	68 (66, 71)	4* (0, 8)
GMT	18 (15, 20)	13 (11, 15)	1.33* § (1.11, 1.6)	36 (29, 45)	27 (21, 33)	1.36* § (1.06, 1.73)	23 (21, 27)	17 (15, 20)	1.34* § (1.15, 1.56)
W-135	N=594	N=605		N=542	N=533		N=1136	N=1138	
% Sero-response‡	72 (68, 75)	58 (54, 62)	14 * § (9, 19)	57 (53, 61)	44 (40, 49)	13* § (7, 18)	65 (62, 67)	51 (48, 54)	13* § (9, 17)
%≥1:8	90 (87, 92)	75 (71, 78)	15* § (11, 19)	91 (88, 93)	84 (81, 87)	7* § (3, 11)	90 (88, 92)	79 (77, 81)	11* § (8, 14)

	2-5 years			6-10 years			2-10 years		
Endpoint by Serogroup	**MENVEO (95% CI)**	**Menactra (95% CI)**	**Percent Difference (MENVEO – Menactra) or GMT ratio (MENVEO/ Menactra) (95% CI)**	**MENVEO (95% CI)**	**Menactra (95% CI)**	**Percent Difference (MENVEO – Menactra) or GMT ratio (MENVEO/ Menactra) (95% CI)**	**MENVEO (95% CI)**	**Menactra (95% CI)**	**Percent Difference (MENVEO – Menactra) or GMT ratio (MENVEO/ Menactra) (95% CI)**
GMT	43 (38, 50)	21 (19, 25)	2.02* § (1.71, 2.39)	61 (52, 72)	35 (30, 42)	1.72* § (1.44, 2.06)	49 (44, 54)	26 (23, 29)	1.87* § (1.65, 2.12)
Y	N=593	N=600		N=545	N=539		N=1138	N=1139	
% Seroresponse‡	66 (62, 70)	45 (41, 49)	21 * § (16, 27)	58 (54, 62)	39 (35, 44)	19* § (13, 24)	62 (60, 65)	42 (40, 45)	20* § (16, 24)
%≥1:8	76 (72, 79)	57 (53, 61)	19* § (14, 24)	79 (76, 83)	63 (59, 67)	16* § (11, 21)	77 (75, 80)	60 (57, 63)	18* § (14, 21)
GMT	24 (20, 28)	10 (8.68, 12)	2.36* § (1.95, 2.85)	34 (28, 41)	14 (12, 17)	2.41* § (1.95, 2.97)	29 (25, 32)	12 (11, 14)	2.37* § (2.06, 2.73)

‡ Seroresponse was defined as: a) post vaccination hSBA ≥1:8 for subjects with a pre-vaccination hSBA <1:4; or, b) at least 4-fold higher than baseline titres for subjects with a pre-vaccination hSBA ≥1:4.
* Non-inferiority criterion met (the lower limit of the two-sided 95% CI >-10 % for vaccine group differences [MENVEO minus Menactra] and > 0.5 for ratio of GMTs [MENVEO/Menactra]).
§ Immune response was statistically higher (the lower limit of the two-sided 95% CI >0% for vaccine group differences or > 1.0 for ratio of GMTs); however, the clinical relevance of higher post-vaccination immune responses is not known

In the same study, a separate group of children, 2 through 5 years of age (N=297) in the per protocol population were immunised with two doses of MENVEO, two months apart. The observed seroresponse rates (with 95% CI) at 1 month after the second dose were: 91% (87-94), 98% (95-99), 89% (85-92), and 95% (91-97) for serogroups A, C, W-135 and Y, respectively. The proportion of subjects with hSBA ≥ 1:8 (95% CI) were 91% (88-94), 99% (97-100), 99% (98-100), and 98% (95-99) for serogroups A, C, W-135 and Y, respectively. The hSBA GMTs (95% CI) for this group were 64 (51-81), 144 (118-177), 132 (111-157), and 102 (82-126) for serogroups A, C, W-135 and Y, respectively.

Persistence of immune response and booster response in children (2-10 years of age)

Persistence of immune response 1 year after primary vaccination with MENVEO was evaluated in study V59P8. At 1-year post vaccination, MENVEO continued to be statistically higher than Menomune for serogroups A, W-135 and Y, as measured by percentage of subjects with hSBA≥1:8 and GMTs. MENVEO was non-inferior on these endpoints for serogroup C (Table 9).

Table 9: Comparison of serum bactericidal antibody responses to MENVEO and Menomune 1 month and 12 months after vaccination of subjects 2 through 10 years of age.

Endpoint by Serogroup	**MENVEO (95% CI)**	**Menomune (95% CI)**	**Percent Difference (MENVEO – Menomune) or GMT ratio (MENVEO/ Menomune-PS) (95% CI)**	**MENVEO (95% CI)**	**Menomune (95% CI)**	**Percent Difference (MENVEO – Menomune) or GMT ratio (MENVEO/ Menomune) (95% CI)**
	1-month post-vaccination			12-months post-vaccination		
A	N=280	N=281		N=253	N=238	
Seroresponse‡	79 (74, 84)	37 (31, 43)	43 *§ (35,50)	n/a	n/a	
%≥1:8	79 (74, 84)	37 (31, 43)	42 *§ (35, 49)	23 (18, 29)	13 (9, 18)	10 *§ (3, 17)
GMT	36 (30, 44)	6.31 (5.21, 7.64)	5.74*§ (4.38, 7.53)	3.88 (3.39, 4.44)	3 (2.61, 3.44)	1.29 *§ (1.07, 1.57)
C	N=281	N=283		N=252	N=240	
Seroresponse‡	64 (59, 70)	43 (38, 49)	21*§ (13, 29)	n/a	n/a	
%≥1:8	73 (68, 78)	54 (48, 60)	19 *§ (11, 27)	53 (47, 59)	44 (38, 51)	9 * (0, 18)
GMT	26 (21, 34)	15 (12, 20)	1.71*§ (1.22, 2.40)	11 (8.64, 13)	9.02 (7.23, 11)	1.19* (0.87, 1.62)
W-135	N=279	N=282		N=249	N=237	
Seroresponse‡	67 (61, 72)	31 (26, 37)	35 *§ (28, 43)	n/a	n/a	
%≥1:8	92 (88, 95)	66 (60, 71)	26 *§ (20, 33)	90 (86, 94)	45 (38, 51)	46 *§ (38, 53)
GMT	60 (50, 71)	14 (12, 17)	4.26*§ (3.35, 5.43)	42 (35, 50)	7.57 (6.33, 9.07)	5.56 *§ (4.32, 7.15)
Y	N=280	N=282		N=250	N=239	
Seroresponse‡	75 (70, 80)	38 (32, 44)	37 *§ (30, 45)	n/a	n/a	

Endpoint by Serogroup	MENVEO (95% CI)	Menomune (95% CI)	Percent Difference (MENVEO – Menomune) or GMT ratio (MENVEO/ Menomune-PS) (95% CI)	MENVEO (95% CI)	Menomune (95% CI)	Percent Difference (MENVEO – Menomune) or GMT ratio (MENVEO/ Menomune) (95% CI)
	1-month post-vaccination			12-months post-vaccination		
%≥1:8	88 (83, 91)	53 (47, 59)	34*§ (27, 41)	77 (71, 82)	32 (26, 38)	45 *§ (37, 53)
GMT	54 (44, 66)	11 (9.29, 14)	4.70 *§ (3.49, 6.31)	27 (22, 33)	5.29 (4.34, 6.45)	5.12 *§ (3.88, 6.76)

‡ Seroresponse was defined as: a) post vaccination hSBA ≥1:8 for subjects with a pre-vaccination hSBA <1:4; or, b) at least 4-fold higher than baseline titres for subjects with a pre-vaccination hSBA ≥1:4.
* Non-inferiority criterion met (the lower limit of the two-sided 95% CI >-10 % for vaccine group differences [MENVEO minus Menomune] and > 0.5 for ratio of GMTs [MENVEO/Menomune]).
§ Immune response was statistically higher (the lower limit of the two-sided 95% CI >0% for vaccine group differences or > 1.0 for ratio of GMTs); however, the clinical relevance of higher post-vaccination immune responses is not known.
n/a = not applicable

Antibody persistence at 5 years after primary vaccination was assessed in the extension study V59P20E1. There was substantial antibody persistence observed against serogroups C, W and Y, with the percentages of subjects with hSBA ≥ 1:8 being 32% and 56% against serogroup C in subjects 2-5 and 6-10 years of age, respectively, 74% and 80% against serogroup W, and 48% and 53% against serogroup Y. GMTs were respectively 6.5 and 12 for serogroup C, 19 and 26 for serogroup W, and 8.13 and 10 for serogroup Y. For serogroup A, 14% and 22% of subjects 2-5 and 6-10 years of age, respectively, had hSBA ≥ 1:8 (GMTs 2.95 and 3.73). Levels for all serogroups were higher than those seen in meningococcal vaccine-naïve children of similar ages. The children also received a booster dose of MENVEO, 5 years after a single dose primary vaccination. All subjects in both age groups had hSBA ≥ 1:8 across serogroups, with antibody titres several fold higher than seen after the primary vaccination (Table 10).

Table 10: Persistence of immune responses 5 years after primary vaccination with MENVEO, and immune responses 1 month after a booster dose among subjects aged 2 - 5 years and 6 -10 years at the time of primary vaccination

Serogroup	2-5 years				6-10 years			
	5-year persistence		1 month after booster		5-year persistence		1 month after booster	
	%hSBA ≥1:8 (95% CI)	hSBA GMTs (95% CI)	%hSBA ≥1:8 (95% CI)	hSBA GMTs (95% CI)	%hSBA ≥1:8 (95% CI)	hSBA GMTs (95% CI)	%hSBA ≥1:8 (95% CI)	hSBA GMTs (95% CI)
A	N=96	N=96	N=95	N=95	N=64	N=64	N=60	N=60

Serogroup	2-5 years				6-10 years			
	5-year persistence		1 month after booster		5-year persistence		1 month after booster	
	%hSBA ≥1:8 (95% CI)	hSBA GMTs (95% CI)	%hSBA ≥1:8 (95% CI)	hSBA GMTs (95% CI)	%hSBA ≥1:8 (95% CI)	hSBA GMTs (95% CI)	%hSBA ≥1:8 (95% CI)	hSBA GMTs (95% CI)
	14 (7, 22)	2.95 (2.42, 3.61)	100 (96, 100)	361 (299, 436)	22 (13, 34)	3.73 (2.74, 5.06	100 (94, 100)	350 (265, 463)
C	N=96	N=96	N=94	N=94	N=64	N=64	N=60	N=60
	32 (23, 43)	6.5 (4.75, 8.9)	100 (96, 100)	498 (406, 610)	56 (43, 69)	12 (7.72, 19)	100 (94, 100)	712 (490, 1036)
W-135	N=96	N=96	N=95	N=95	N=64	N=64	N=60	N=60
	74 (64, 82)	19 (14, 25)	100 (96, 100)	1534 (1255, 1873)	80 (68, 89)	26 (18, 38)	100 (94, 100)	1556 (1083, 2237)
Y	N=96	N=96	N=94	N=94	N=64	N=64	N=59	N=59
	48 (38, 58)	8.13 (6.11, 11)	100 (96, 100)	1693 (1360, 2107)	53 (40, 66)	10 (6.51, 16)	100 (94, 100)	1442 (1050, 1979)

Demonstration of immunologic non-inferiority to Menactra® (Sanofi Pasteur) among subjects aged 11-55 years.

Immunogenicity was evaluated in a Phase 3, randomised, multicentre, active controlled clinical trial V59P13 that enrolled adolescents (11-18 years of age) and adults (19-55 years of age). Participants received either a dose of MENVEO (N = 2649) or Menactra (N = 875). Sera were obtained both before vaccination and 28 days after vaccination. Demographic characteristics between MENVEO and Menactra vaccine groups were comparable within each age group.

Immunogenicity in Adolescents

In the 11 to 18 year old population of the pivotal study, V59P13, noninferiority of MENVEO to Menactra was demonstrated for all four serogroups using the primary endpoint (hSBA seroresponse) and two secondary endpoints, percentage of all subjects with 1-month post-vaccination hSBA ≥ 1:8, and geometric mean titre (GMT). Furthermore, hSBA GMTs for all four serogroups were statistically superior in the MENVEO group, as compared to the Menactra group. The percentages of subjects with hSBA seroresponse and with hSBA≥ 1:8 were statistically superior for serogroups A, W, and Y in the MENVEO group, as compared to the Menactra group (Table 11). The clinical relevance of higher immune responses is uncertain.

Table 11: Comparison of bactericidal antibody responses† to MENVEO and Menactra 28 days after vaccination of subjects aged 11-18 years

	Bactericidal Antibody Response†		**Comparison of MENVEO and Menactra**	
Endpoint by Serogroup	**MENVEO (95% CI)**	**Menactra (95% CI)**	**MENVEO / Menactra (95% CI)**	**MENVEO minus Menactra (95% CI)**
A	N=1075	N=359		
% Seroresponse‡	75 (72, 77)	66 (61, 71)		8 (3, 14)* §
% ≥ 1:8	75 (73 , 78)	67 (62, 72)	-	8 (3, 14)
GMT	29 (24 , 35)	18 (14, 23)	1.63 (1.31, 2.02)	-
C	N=1483	N=501		
% Seroresponse‡	75 (73, 77)	73 (69, 77)		2 (-2, 7)*
% ≥ 1:8	84 (82, 86)	84 (80, 87)	-	1 (-3, 5)

	Bactericidal Antibody Response†		Comparison of MENVEO and Menactra	
Endpoint by Serogroup	**MENVEO (95% CI)**	**Menactra (95% CI)**	**MENVEO / Menactra (95% CI)**	**MENVEO minus Menactra (95% CI)**
GMT	59 (48, 73)	47 (36, 61)	1.27 (1.01, 1.6)	-
W-135	N=1024	N=288		
% Seroresponse‡	75 (72, 77)	63 (57, 68)		12 (6, 18)*§
% ≥ 1:8	96 (95, 97)	88 (84, 92)	-	8 (4, 12)
GMT	87 (74, 102)	44 (35, 54)	2.00 (1.66, 2.42)	-
Y	N=1036	N=294		
% Seroresponse‡	68 (65, 71)	41 (35, 47)		27 (20, 33)* §
% ≥ 1:8	88 (85, 90)	69 (63, 74)	-	19 (14, 25)
GMT	51 (42, 61)	18 (14, 23)	2.82 (2.26, 3.52)	-

† Serum Bactericidal Assay with exogenous human complement source (hSBA). ‡ Seronegative was defined as a pre-vaccination hSBA <1:4. Among the seronegative subjects, the seroresponse endpoint was defined as a post vaccination titre of ≥ 1:8.

* noninferiority criterion met (the lower limit of the two-sided 95% CI >-10 % for vaccine group differences (MENVEO minus Menactra), >0.5 for vaccine group ratios (MENVEO/Menactra)

§ superiority criterion met (the lower limit of two-sided 95% CI >0% for vaccine group differences).

In the non-inferiority study, V59P6, immunogenicity was assessed among adolescents aged 11-17 years who had been randomised to receive either MENVEO or Menomune® (Sanofi Pasteur Ltd), a quadrivalent meningococcal polysaccharide vaccine. Responses to MENVEO were shown to be non-inferior to those to Menomune for all four serogroups (A, C, W and Y) based on seroresponse, proportions achieving hSBA titres ≥ 1:8, and GMTs. At one-year post vaccination, the percentage of MENVEO recipients with hSBA ≥ 1:8 remained significantly higher compared with Menomune recipients for serogroups C, W and Y, and similar between the two study groups for serogroup A (Table 12).

Table 12 Comparison of bactericidal antibody responses† to MENVEO and Menomune 28 days after vaccination of subjects aged 11-17 years.

	Seroresponse			hSBA ≥ 1:8			hSBA GMTs		
	MENVEO	Menomune	Vaccine differences‡	MENVEO	Menomune	MENVEO minus Menomune	MENVEO	Menomune	MENVEO / Menomune †
A	N=148	N=179		N=148	N=179		N=148	N=179	
	80% (73, 86)	41% (34, 49)	39% (29, 48)**	81% (74, 87)	41% (34, 49)	40% (30, 49)*	34 (26, 44)	6.97 (5.51, 8.82)	4.87 (3.41, 6.95)*
C	N=148	N=177		N=148	N=177		N=148	N=177	
	76% (68, 82)	54% (47, 62)	21% (11, 31)**	83% (76, 89)	63% (56, 70)	20% (10, 29)*	58 (39, 85)	30 (21, 43)	1.9 (1.13, 3,19)*
W	N=146	N=173		N=146	N=173		N=146	N=173	
	84% (77, 90)	71% (63, 77)	14% (5, 23)**	90% (84, 95)	86% (80, 91)	4% (-3, 11)*	49 (39, 62)	30 (24, 37)	1.65 (1.22, 2.24)*
Y	N=147	N=177		N=147	N=177		N=147	N=177	
	86% (79, 91)	66% (59, 73)	20% (11, 28)**	95% (90, 98)	81% (74, 86)	14% (7, 21)*	100 (74, 134)	34 (26, 45)	2.91 (1.99, 4.27)*

‡ Difference in proportions for MenACWY minus Menomune.
† Ratio of GMTs for MenACWY to Menomune.
* noninferiority criterion met (the lower limit of the two-sided 95% CI >-10 % for vaccine group differences (MENVEO minus Menomune), >0.5 for vaccine group ratios (MENVEO/Menomune)
** the seroresponse was statistically higher (the lower limit of the two-sided 95% CI >0% for vaccine group differences).

Immunogenicity in Adults

In the 19 to 55-year-old population of the pivotal study, V59P13, noninferiority of responses to MENVEO to those to Menactra was demonstrated for all four serogroups using all three endpoints (seroresponse [primary endpoint], hSBA ≥ 1:8, and hSBA GMTs). Furthermore, both hSBA GMTs and the percentage of subjects with hSBA seroresponse were statistically superior for serogroups C, W, and Y in the MENVEO group, as compared to the Menactra group. The percentage of subjects with hSBA ≥ 1:8 was statistically superior for serogroups C and Y in the MENVEO group, as compared to the Menactra group (Table 13). The clinical relevance of higher immune responses is uncertain.

Table 13: Comparison of bactericidal antibody responses† to MENVEO and Menactra 28 days after vaccination of subjects aged 19-55 years.

	Bactericidal Antibody Response†		Comparison of MENVEO and Menactra	
Endpoint by Serogroup	**MENVEO (95% CI)**	**Menactra (95% CI)**	**MENVEO / Menactra (95% CI)**	**MENVEO minus Menactra (95% CI)**
A	N=963	N=321		
% Seroresponse‡	67 (64, 70)	68 (63, 73)		-1 (-7, 5)*
% ≥ 1:8	69 (66, 72)	71 (65, 76)	-	-2 (-7, 4)
GMT	31 (27, 36)	30 (24, 37)	1.06 (0.82, 1.37)	-
C	N=961	N=318		
% Seroresponse‡	67 (64, 70)	58 (53, 64)		9 (3, 15)* §
% ≥ 1:8	80 (77, 83)	72 (67, 77)	-	8 (3, 14)
GMT	52 (44, 60)	32 (25, 40)	1.63 (1.24, 2.13)	-
W-135	N=484	N=292		
% Seroresponse‡	50 (46, 55)	41 (35, 47)		9 (2, 17)* §
% ≥ 1:8	94 (91, 96)	90 (86, 93)	-	4 (0, 9)
GMT	111 (93, 132)	69 (55, 85)	1.61 (1.24, 2.1)	-
Y	N=503	N=306		
% Seroresponse‡	56 (51, 60)	40 (34, 46)		16 (9, 23)* §
% ≥ 1:8	79 (76, 83)	70 (65, 75)	-	9 (3, 15)
GMT	44 (37, 52)	21 (17, 26)	2.10 (1.60, 2.75)	-

† Serum Bactericidal Assay with exogenous human complement source (hSBA).

‡ Seronegative was defined as a pre-vaccination hSBA <1:4. Among the seronegative subjects, the seroresponse endpoint was defined as a post vaccination titre of ≥ 1:8.

* noninferiority criterion met (the lower limit of the two-sided 95% CI >-10 % for vaccine group differences (MENVEO minus Menactra), >0.5 for vaccine group ratios (MENVEO/Menactra))

§ superiority criterion met (the lower limit of two-sided 95% CI >0% for vaccine group difference).

5.2 PHARMACOKINETIC PROPERTIES

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity studies have not been performed with MENVEO.

Carcinogenicity

Carcinogenesis and mutagenesis studies have not been performed with MENVEO.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Vial containing MenA lyophilised conjugate component:

- Sucrose
- Potassium dihydrogen phosphate

Vial or Syringe containing MenCWY liquid conjugate component:

- Sodium phosphate monobasic monohydrate
- Dibasic sodium phosphate dihydrate
- Sodium chloride
- Water for Injections

6.2 INCOMPATIBILITIES

The medicinal product must not be admixed with other medicinal products (See Section 4.5 – INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store between 2° and 8°C away from a freezer compartment. DO NOT FREEZE. Product that has been frozen should not be used. Keep the MenA (vial) and MenCWY (syringe or vial) components in the outer carton in order to protect from light. Do not use after the expiry date.

Following reconstitution, to reduce microbiological hazard the product should be used as soon as practicable after reconstitution. If storage is necessary, hold at 2-8 °C for not more than 24 hours. The two components of the product may have different expiry dates. The outer carton bears the earlier of the two dates and the product should be used before this date. The carton and ALL of its contents must be discarded on reaching this outer carton expiry date.

6.5 NATURE AND CONTENTS OF CONTAINER

MENVEO is presented in a Type I glass vial containing the MenA lyophilised conjugate component with a butyl rubber stopper.

The MenCWY liquid conjugate component is presented either in a Type I glass syringe or a Type I glass vial. The syringe has a tip cap (Type I elastomeric closure with 10% of Dry Natural rubber). The vial has a butyl rubber stopper.

The vial/syringe presentation is presented in single-dose packs. The vial/vial presentation is presented in single-dose (2 vials) and 5-doses (10 vials) multi-packs.

Not all presentations and pack sizes may be marketed.

One dose (0.5 mL of the reconstituted vaccine) contains:

Meningococcal oligosaccharide – group A*	10 micrograms
Conjugated to *Corynebacterium diphtheriae* CRM_{197} protein	16.7 to 33.3 micrograms
Meningococcal oligosaccharide - group C*	5 micrograms
Conjugated to *Corynebacterium diphtheriae* CRM_{197} protein	7.1 to 12.5 micrograms
Meningococcal oligosaccharide - group W-135*	5 micrograms
Conjugated to *Corynebacterium diphtheriae* CRM_{197} protein	3.3 to 8.3 micrograms
Meningococcal oligosaccharide - group Y*	5 micrograms

Conjugated to *Corynebacterium diphtheriae* CRM_{197} protein	5.6 to 10 micrograms

*Prepared from *Neisseria meningitidis*

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

N/A

CAS number

N/A

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8. SPONSOR

GlaxoSmithKline Australia Pty Ltd
Level 4,
436 Johnston Street
Abbotsford, Victoria, 3067

9. DATE OF FIRST APPROVAL

20 May 2010

10. DATE OF REVISION:

30 March 2020

Summary table of changes

Section changed	Summary of new information
4.8	Addition of local lymphadenopathy as a new adverse reaction in the post-marketing section.

Version 9.0