AUSTRALIAN PRODUCT INFORMATION – NIMENRIX® (Meningococcal polysaccharide groups A, C, W-135 and Y conjugate vaccine)

1 NAME OF THE MEDICINE

Meningococcal polysaccharide groups A, C, W-135 and Y conjugate vaccine.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

NIMENRIX powder and solvent for solution for injection in pre-filled syringe.

After reconstitution, 1 dose (0.5 mL) contains:

Meningococcal polysaccharide - Group A*	5 micrograms
Meningococcal polysaccharide - Group C*	5 micrograms
Meningococcal polysaccharide - Group W-135*	5 micrograms
Meningococcal polysaccharide - Group Y*	5 micrograms
*conjugated to tetanus toxoid carrier protein	44 micrograms

For the full list of excipients, see Section 6.1 List of excipients.

No preservative or adjuvant is added.

3 PHARMACEUTICAL FORM

NIMENRIX is supplied as a white powder in a glass vial, together with a clear and colourless solvent supplied in a pre-filled syringe or ampoule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

NIMENRIX is indicated for active immunisation of individuals from 6 weeks of age against invasive meningococcal diseases caused by *Neisseria meningitidis* groups A, C, W-135 and Y.

4.2 Dose and method of administration

NIMENRIX should be used in accordance with available official recommendations.

Dosage

Infants from 6 to 12 weeks of age

The recommended immunisation series consists of three doses, each of 0.5 ml. The primary infant series consists of two doses, with the first dose given from 6 weeks of age and with an interval of 2 months between doses. The third (booster) dose is recommended at 12 months of age (see Section 5.1 Pharmacodynamic properties).

Children from 12 months of age, adolescents and adults

A single 0.5 mL dose should be administered

A second dose of NIMENRIX may be considered appropriate for some individuals (see Section 4.4 Special warnings and precautions for use).

NIMENRIX may be given as a booster dose to individuals who have previously received primary vaccination with NIMENRIX or other conjugated or plain polysaccharide meningococcal vaccines (see Sections 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties).

NIMENRIXMethod of administration

NIMENRIX is for single use in one patient only.

NIMENRIX is for intramuscular injection only.

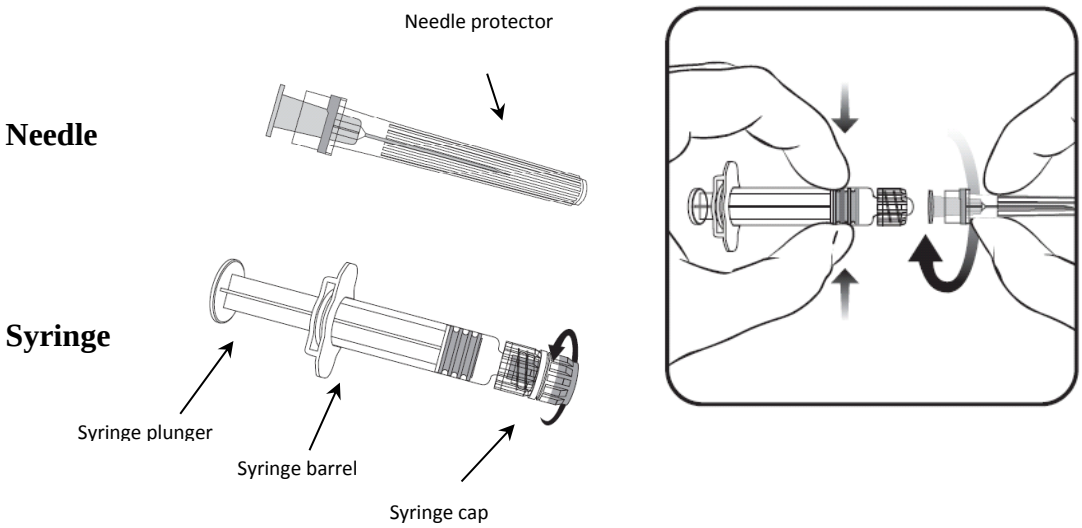
The injection sites are the anterolateral aspect of the thigh in infants or the anterolateral aspect of the thigh or deltoid muscle in individuals from 1 year of age (see Sections 4.4 Special warnings and precautions for use and 4.5 Interactions with other medicines).

Use and handling

Instructions for reconstitution of the vaccine with the solvent presented in pre-filled syringe

NIMENRIX must be reconstituted by adding the entire contents of the pre-filled syringe of solvent to the vial containing the powder.

To attach the needle to the syringe, refer to the picture below.



1. Holding the syringe barrel in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.
2. To attach a screw-thread needle to the syringe, twist the needle clockwise into the syringe until you feel it lock (see picture). A needle without a screw-thread may also be used. In this case, the needle should be attached without screwing.
3. Remove the needle protector, which on occasion can be a little stiff.
4. Add the solvent to the powder. After the addition of the solvent to the powder, the mixture should be well shaken until the powder is completely dissolved in the solvent.

The reconstituted vaccine is a clear colourless solution.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of physical aspect prior to administration. In the event of either being observed, discard the vaccine.

After reconstitution, the vaccine should be used promptly. Although delay is not recommended, stability has been demonstrated for 8 hours at 30°C after reconstitution. If not used within 8 hours, do not administer the vaccine.

A new needle should be used to administer the vaccine.

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

Instructions for reconstitution of the vaccine with solvent presented in ampoules

NIMENRIX must be reconstituted by adding the entire content of the ampoule of solvent to the vial containing the powder. To do so, break the top of the ampoule, draw up the solvent with a syringe and add the solvent to the powder. The mixture should be well shaken until the powder is completely dissolved in the solvent.

The reconstituted vaccine is a clear colourless solution.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of physical aspect prior to administration. In the event of either being observed, discard the vaccine.

After reconstitution, the vaccine should be used promptly. Although delay is not recommended, stability has been demonstrated for 8 hours at 30°C after reconstitution. If not used within 8 hours, do not administer the vaccine.

A new needle should be used to administer the vaccine.

4.3 Contraindications

NIMENRIX should not be administered to subjects with hypersensitivity to the active substances or to any of the excipients contained in the vaccine.

4.4 Special warnings and precautions for use

NIMENRIX should under no circumstances be administered intravascularly, intradermally or subcutaneously.

It is good clinical practice to precede vaccination by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable effects) and a clinical examination.

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

Intercurrent illness

As with other vaccines, vaccination with NIMENRIX should be postponed in subjects suffering from an acute severe febrile illness. The presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

Syncope

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

Thrombocytopenia and coagulation disorders

As with other vaccines administered intramuscularly, NIMENRIX should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects.

Immunodeficiency

It may be expected that in patients receiving immunosuppressive treatment or patients with immunodeficiency, an adequate immune response may not be elicited.

Persons with certain complement deficiencies and persons receiving treatment that inhibits terminal complement activation (for example, eculizumab) are at increased risk for invasive disease caused by *Meningococcal polysaccharide* serogroups A, C, W-135 and Y even if they develop antibodies following vaccination with NIMENRIX.

Special populations

Safety and immunogenicity data are available for a limited number of individuals with increased susceptibility to meningococcal infection due to anatomic or functional asplenia (such as sickle cell disease) (see 4.8 Adverse effects and 5.1 Pharmacodynamic properties).

Protection against meningococcal disease

NIMENRIX will only confer protection against *Neisseria meningitidis* groups A, C, W-135 and Y. The vaccine will not protect against other *Neisseria meningitidis* groups.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

Immune responses in toddlers aged 12-14 months

At one month post vaccination, toddlers aged 12-14 months had similar rSBA responses to groups A, C, W-135 and Y following one dose of NIMENRIX or two doses of NIMENRIX given two months apart. At one year post vaccination, the rSBA responses for groups A, C, W-135 and Y were similar in both the one and the two dose groups (see Section 5.1 Pharmacodynamic properties).

Measured with a serum bactericidal assay using human complement (hSBA), 1 month post vaccination, responses to groups W-135 and Y were lower after a single dose than after 2 doses given two months apart, while responses to groups A and C were similar in the two groups (see Section 5.1 Pharmacodynamic properties). The clinical relevance of these findings is unknown. If a toddler is expected to be at immediate risk of invasive meningococcal disease due to the exposure to groups W-135 and Y, consideration may be given to administering a second dose after an interval of 2 months. At one year post vaccination, the hSBA responses for groups A, C, W-135 and Y were similar in both the one and the two dose groups (see Section 5.1 Pharmacodynamic properties). Regarding waning of antibody against MenA or MenC after a first dose of NIMENRIX in children aged 12-23 months, see under Persistence of serum bactericidal antibody titres.

Persistence of serum bactericidal antibody titres

Persistence of antibodies has been evaluated up to 5 years after vaccination. The persistence studies with NIMENRIX have shown a waning of serum bactericidal antibody titres against MenA when using human complement in the assay (hSBA) (see Section 5.1 Clinical Trials). The clinical relevance of the waning of hSBA-MenA antibody titres is unknown.

Currently there is limited information available on the safety of a booster dose. However, if an individual is expected to be at particular risk of exposure to MenA and received a dose of NIMENRIX more than approximately one year previously, consideration may be given to administering a booster dose.

Similar to the monovalent Men C comparator, a decline in antibody titres over time has been observed. The clinical relevance of the waning antibody titres is unknown. A booster dose might be considered in individuals vaccinated at toddler age remaining at high risk of exposure to meningococcal disease caused by groups A, C, W-135 and Y (see Section 5.1 Pharmacodynamic properties).

Although NIMENRIX contains tetanus toxoid, this vaccine does not substitute for tetanus immunisation.

Use in the elderly

No data available.

Paediatric Use

See Sections 4.1 Therapeutic indications; 4.2 Dose and method of administration; 4.4 Special warnings and precautions for use (see under Protection against meningococcal disease); 4.5 Interactions with other medicines and other forms of interactions; 4.8 Adverse effects and 5.1 Pharmacodynamic properties.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

In infants, NIMENRIX can be given concomitantly with combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliovirus and Haemophilus influenzae type b vaccines, as well as 10-valent pneumococcal conjugate vaccine.

From age 1 and above, NIMENRIX can be given concomitantly with any of the following vaccines: hepatitis A (HAV) and hepatitis B (HBV) vaccines, measles-mumps-rubella (MMR) vaccine, measles-mumps-rubella-varicella (MMRV) vaccine, 10-valent pneumococcal conjugate vaccine or unadjuvanted seasonal influenza vaccine.

NIMENRIX can also be given concomitantly with combined diphtheria-tetanus-acellular pertussis (DTaP) vaccines, including combination DTaP vaccines with hepatitis B, inactivated polio (IPV) or Haemophilus influenzae type b (Hib), such as DTaP-HBV-IPV/Hib vaccine and 13-valent pneumococcal conjugate vaccine in the second year of life.

In individuals aged 9 to 25 years, NIMENRIX can be given concomitantly with human papillomavirus bivalent [Type 16 and 18] vaccine, recombinant (HPV2).

Safety and immunogenicity of NIMENRIX was evaluated when sequentially administered or co-administered with a DTaP-HBV-IPV/Hib vaccine in the second year of life. The administration of NIMENRIX one month after the DTaP-HBV-IPV/Hib vaccine resulted in lower MenA, MenC and MenW-135 GMTs as measured with rSBA. Clinical relevance of this observation is unknown, since at least 99.4% of subjects (N=178) had rSBA titres ≥ 8 for each group (A, C, W-135, Y). Whenever possible, NIMENRIX and a tetanus toxoid (TT) containing vaccine, such as DTaP-HBV-IPV/Hib vaccine, should either be co-administered or NIMENRIX should be administered at least one month before the TT-containing vaccine.

One month after co-administration with a 10-valent pneumococcal conjugate vaccine, lower Geometric Mean antibody Concentrations (GMCs) and opsonophagocytic assay (OPA) antibody GMTs were observed for one pneumococcal serotype (18C conjugated to tetanus toxoid carrier protein). Clinical relevance of this observation is unknown. There was no impact of co-administration on the other nine pneumococcal serotypes.

One month after co-administration with a combined tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed (Tdap) in subjects aged 11 to 25 years, lower GMCs were observed to each pertussis antigen (pertussis toxoid[PT], filamentous haemagglutinin [FHA] and pertactin [PRN]). More than 98% of subjects had anti-PT, FHA or PRN concentrations above the assay cut-off thresholds. The clinical relevance of these observations is unknown. There was no impact of co-administration on immune responses to NIMENRIX or the tetanus or diphtheria antigens included in Tdap.

If NIMENRIX is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

As with other vaccines it may be expected that in patients receiving immunosuppressive treatment an adequate response may not be elicited.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Animal studies with NIMENRIX do not indicate direct or indirect harmful effects with respect to fertility (see Section 5.3 Preclinical safety data).

Use in pregnancy - Pregnancy Category B2

There is limited experience with use of NIMENRIX in pregnant women.

Animal studies with NIMENRIX do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see Section 5.3 Preclinical safety data).

NIMENRIX should be used during pregnancy only when clearly needed, and the possible advantages outweigh the potential risks for the foetus.

Use in lactation

The safety of NIMENRIX when administered to breastfeeding women has not been evaluated. It is unknown whether NIMENRIX is excreted in human breast milk.

NIMENRIX should only be used during breast-feeding when the possible advantages outweigh the potential risks.

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (undesirable effects)

Clinical trial data

The safety of NIMENRIX presented in the table below is based on two clinical study datasets as follows:

- A pooled analysis of data from 9,621 subjects administered a single dose of NIMENRIX. This total included 3,079 toddlers (12 months to 23 months), 909 children between 2 and 5 years of age, 990 children between 6 and 10 years of age, 2,317 adolescents (11 to 17 years) and 2,326 adults (18 to 55 years). In a separate study a single dose of NIMENRIX was administered to 274 individuals aged 56 years and older.
- Data from a study in infants aged 6 to 12 weeks at the time of the first dose (Study MenACWY-TT-083), 1,052 subjects received at least one dose of a primary series of 2 or 3 doses of NIMENRIX and 1,008 received a booster dose at approximately 12 months of age.

Local and general adverse reactions

In all age groups, the local adverse reactions of pain, redness and swelling at the injection site were reported at a very common frequency after vaccination.

In the infant and toddler groups, the general adverse reactions of drowsiness, fever, irritability/fussiness and loss of appetite were reported at a very common frequency after vaccination.

In an additional clinical study of age matched subjects who were either healthy or at increased risk of meningococcal disease due to anatomical or functional asplenia (such as sickle cell disease), the safety profile of NIMENRIX in at-risk children and adolescents was generally similar to that observed in the non-asplenic population (see 5.1 Pharmacodynamic properties).

In the 12-14 months age group who received 2 doses of NIMENRIX given 2 months apart, the first and second doses were associated with similar local and systemic reactogenicity.

The 2–5 year group reported general adverse reactions at a frequency ranging from common (irritability, loss of appetite and fever) to very common (drowsiness).

In the 6-10, 11-17 and ≥ 18 years age groups, the general adverse reactions were reported at a frequency ranging from common (gastrointestinal symptoms and fever) to very common (headache and fatigue).

In a clinical study of 11 to 25 year old subjects co-administered NIMENRIX and Tdap or given the vaccines separately, the local reactions (injection site pain, redness, and swelling) and general reactions (fatigue and headache) occurred at a similar frequency in both groups and in the subjects in the pooled analysis (very common). The general reactions gastrointestinal events (nausea, vomiting, diarrhoea, abdominal pain) occurred more frequently (very common) and fever occurred less frequently (common) compared to subjects in the pooled analysis, but occurred at a similar frequency in subjects co-administered the vaccines and subjects given the vaccines separately in the study.

In a clinical study of female subjects 9 to 25 years old, the local reactions (pain, redness, and swelling at the NIMENRIX injection site) and general reactions (headache, fever, and fatigue) occurred at a similar frequency in subjects co-administered NIMENRIX, Tdap and HPV2 and in subjects given NIMENRIX alone, as they did in subjects in the pooled analysis (very common). The general reactions gastrointestinal events (nausea, vomiting, diarrhoea, abdominal pain) and myalgia occurred at a similar frequency in the 2 groups but more frequently than in the pooled analysis (very common), as did the general reaction rash (common).

Adverse reactions reported are listed according to the following frequency:

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

Unknown (cannot be estimated from the available data)

<u>Metabolism and nutrition disorders</u>
Very common: appetite lost

<u>Psychiatric disorders</u>
Very common: irritability
Uncommon: insomnia, crying

<u>Nervous system disorders</u>
Very common: drowsiness, headache
Uncommon: hypoaesthesia, dizziness

<u>Gastrointestinal disorders</u>
Common: gastrointestinal symptoms (including diarrhoea, vomiting and nausea*)

Skin and subcutaneous tissue disorders
Uncommon: pruritus, rash**

Musculosckeletal and connective tissue disorders
Uncommon: myalgia, pain in extremity

General disorders and administration site conditions
Very common: fever, swelling, pain and redness at injection site, fatigue
Common: injection site haematoma*
Uncommon: malaise, injection site reaction (including induration, pruritus, warmth, anaesthesia)

*Nausea and injection site haematoma occurred at a frequency of Uncommon in infants
**Rash occurred at a frequency of Common in infants
The adverse reactions headache, hypoaesthesia, dizziness, pruritus, myalgia, pain in extremity and fatigue were not reported in the infant clinical study.

Post-marketing experience

General disorders and administration site conditions

Unknown: extensive limb swelling at the injection site, frequently associated with erythema, sometimes involving the adjacent joint or swelling of the entire injected limb

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 http://www.tga.gov.au/reporting-problems.

4.9 Overdose

No cases of overdose have been reported.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Anti-capsular meningococcal antibodies protect against meningococcal diseases via complement mediated bactericidal activity. NIMENRIX induces the production of bactericidal antibodies against capsular polysaccharides of groups A, C, W-135 and Y when measured by serum bactericidal antibody assays (SBA) using either rabbit complement

(rSBA) or human complement (hSBA). By conjugating capsular polysaccharide to a protein carrier that contains T-cell epitopes, meningococcal conjugate vaccines like NIMENRIX change the nature of the immune response to capsular polysaccharide from T-cell independent to T-cell dependent.

Clinical trials

Immunogenicity

The immunogenicity of one dose of NIMENRIX has been evaluated in more than 8,000 subjects from 12 months of age and in approximately 1000 subjects below 12 months of age.

Vaccine efficacy was inferred from the demonstration of immunologic non-inferiority compared to licensed meningococcal vaccines. Immunogenicity was measured by rSBA or hSBA which are biomarkers for protective efficacy against meningococcal groups A, C, W-135 and Y.

Persistence of immune response

The persistence of the immune response elicited by NIMENRIX was evaluated up to 5 years after vaccination in subjects aged 12 months to 55 years at the time of vaccination.

In all age groups at all persistence time-points measured, the rSBA GMTs remained higher than prior to vaccination for the four groups (A, C, W-135, Y).

The antibodies elicited by NIMENRIX was similar or higher than those induced by the licensed comparator meningococcal vaccines (Tables 8, 9, 10, 11, 12 and 13).

In contrast to the observed rSBA-MenA persistence across age groups, there was a rapid waning (as measured at 12 months post-dose onwards) of serum bactericidal antibody titres against MenA than other groups (C, W-135, Y) when using human complement in the assay (Tables 8, 9, 10, 11 and 13). This rapid waning of hSBA-MenA antibodies has also been observed with other meningococcal vaccines. The clinical relevance of the rapid waning of hSBA-MenA antibody titres is unknown (see Section 4.4 Special warnings and precautions for use).

The vaccine response was defined in clinical studies as:

rSBA

- Toddlers aged 12-23 months: rSBA $\geq$ 1:8
- Children aged > 2 years, adolescents and adults: rSBA $\geq$ 1:32 for initially seronegative subjects; or at least a 4-fold increase in rSBA titres from pre- to post-vaccination for initially seropositive subjects

hSBA

- At least a 2-fold increase in hSBA titre (i.e hSBA $\geq$1:8) from pre- to post-vaccination for initially seronegative subjects of all ages
- At least a 4-fold increase in hSBA titre from pre- to post-vaccination.for initially seropositive subjects of all ages

Vaccine Immunogenicity

Booster Response

In 5 clinical trials, the use of NIMENRIX as a booster following primary vaccination with NIMENRIX or other meningococcal vaccines (quadrivalent meningococcal A, C, W-135, and Y-DT conjugate vaccine or monovalent MenC conjugate vaccines) was evaluated. A robust NIMENRIX booster response was observed for all groups in all age ranges assessed.

Infants

Immunogenicity in infants

In the clinical study in infants (MenACWY-TT-083), the immunogenicity of a 2-dose primary vaccination schedule was evaluated (Table 1). The doses were administered at 2 and 4 months of age. Routinely used infant vaccines DTPa-HBV-IPV/Hib and a 10-valent pneumococcal vaccine were co-administered. For group C, the immune response elicited by NIMENRIX was compared to a 2-dose priming with licensed monovalent meningococcal conjugate group C vaccines, C-CRM_{197} conjugate (MenC-CRM) and C-TT conjugate (MenC-TT) vaccines. NIMENRIX elicited a bactericidal antibody response against the four groups. The response against group C was non-inferior to the one elicited by the licensed MenC-CRM and MenC-TT vaccines in term of rSBA titres ≥8.

Booster vaccination after priming in infancy:

For subjects primed in infancy with NIMENRIX at 2 and 4 months of age and receiving a NIMENRIX booster dose at 12 months of age, the increase in rSBA and hSBA titres one month post-booster dose ranged between 15 and 80-fold for all groups (study MenACWY-TT-083) and more than 99.0% of all infants achieved post-booster titres above 8 for both assays (Table 1). The observed booster response for MenC was similar to that observed in subjects primed and boosted with a monovalent MenC conjugate vaccine (TT or CRM conjugated) (study MenACWY-TT-083).

Table 1: Bactericidal antibody responses in infants after priming and after a booster dose

Group	Response to		Study MenACWY-TT-083 (2-dose priming) rSBA*			Study MenACWY-TT-083 (2-dose priming) hSBA**		
			N	≥8 (95% CI)	GMT (95% CI)	N	≥8 (95% CI)	GMT (95% CI)
A	NIMENRIX	Post dose 2	456	97.4% (95.4; 98.6)	203 (182; 227)	202	96.5% (93.0; 98.6)	157 (131; 188)
A	NIMENRIX	Booster dose	462	99.6% (98.4; 99.9)	1561 (1412.3; 11725.3)	214	99.5% (97.4;100)	1007.2 (835.7;1213.8)
C	NIMENRIX	Post dose 2	456	98.7% (97.2; 99.5)	612 (540; 693)	218	98.6% (96.0; 99.7)	1308 (1052; 1627)
		Booster dose	463	99.8% (98.8; 100)	1177 (1059.1; 1308)	221	99.5% (97.5; 100)	4992.3 (4085.7; 6100)
	MenC-CRM vaccine	Post dose 2	455	99.6% (98.4; 99.9)	958 (850; 1079)	202	100% (98.2; 100)	3188 (2646; 3841)
		Booster dose	446	98.4% (96.8; 99.4)	1051.4 (919.6; 1201.1)	216	100% (98.3; 100)	5438.2 (4412.4; 6702.3)
	MenC-TT vaccine	Post dose 2	457	100% (99.2; 100)	1188 (1080; 1307)	226	100% (98.4; 100)	2626 (2219; 3109)
		Booster dose	459	100% (99.2; 100)	1960.2 (1776.4; 2163.1)	219	100% (98.3; 100)	5542.3 (4765.2; 6446.2)
W	NIMENRIX	Post dose 2	455	99.1% (97.8; 99.8)	1605 (1383; 1862)	217	100% (98.3; 100)	753 (644; 882)
		Booster dose	462	99.8% (98.8; 100)	2777.2 (2485.1; 3103.6)	218	100% (98.3; 100)	5122.7 (4504.2; 5826.1)
Y	NIMENRIX	Post dose 2	456	98.2% (96.6; 99.2)	483 (419; 558)	214	97.7% (94.6; 99.2)	328 (276; 390)
		Booster dose	462	99.4% (99.1; 99.9)	881.3 (787.5; 986.4)	217	100% (98.3; 100)	2954 (2497.9; 3493.3)

The analysis of immunogenicity was conducted on the primary according-to-protocol (ATP) cohort for immunogenicity.

*rSBA testing performed at Public Health England (PHE) laboratories in UK

**hSBA tested at GSK laboratories

Toddlers

Immunogenicity in toddlers aged 12-23 months

In clinical studies MenACWY-TT-039 and MenACWY-TT-040, the immune response to vaccination with one dose of NIMENRIX or a licensed meningococcal C-CRM_{197} conjugate (MenC-CRM) vaccine was evaluated.

NIMENRIX elicited a protective bactericidal antibody response against the four groups in both studies, with a response against group C that was comparable to the one elicited by the licensed MenC-CRM vaccine in terms of rSBA titres ≥8 (Table 2).

Table 2: Bactericidal antibody responses (rSBA*) in toddlers aged 12-23 months

Group	Response to	Study MenACWY-TT-039 rSBA[(1)]			Study MenACWY-TT-040 rSBA[(2)]		
		N	≥8 (95%CI)	GMT (95%CI)	N	≥8 (95%CI)	GMT (95%CI)
A	NIMENRIX	354	99.7% (98.4; 100)	2205 (2008; 2422)	183	98.4% (95.3; 99.7)	3170 (2577; 3899)
C	NIMENRIX	354	99.7% (98.4; 100)	478 (437; 522)	183	97.3% (93.7; 99.1)	829 (672; 1021)
	MenC-CRM	121	97.5% (92.9; 99.5)	212 (170; 265)	114	98.2% (93.8; 99.8)	691 (521; 918)
W-135	NIMENRIX	354	100% (99.0; 100)	2682 (2453; 2932)	186	98.4% (95.4; 99.7)	4022 (3269; 4949)
Y	NIMENRIX	354	100% (99.0; 100)	2729 (2473; 3013)	185	97.3% (93.8; 99.1)	3168 (2522; 3979)

The analysis of immunogenicity was conducted on the according-to-protocol (ATP) cohorts for immunogenicity.

(1) blood sampling performed 42 to 56 days post vaccination

(2) blood sampling performed 30 to 42 days post vaccination

* tested at GSK laboratories

N = number of subjects with available results

GMT = geometric mean antibody titre

In the study MenACWY-TT-039, the serum bactericidal activity was also measured using human serum as the source of complement (hSBA) as a secondary endpoint (Table 3).

Table 3: Bactericidal antibody responses (hSBA*) in toddlers aged 12-23 months

Group	Response to	N	Study MenACWY-TT-039 hSBA[(1)*]	
			≥8 (95% CI)	GMT (95%CI)
A	NIMENRIX	338	77.2% (72.4; 81.6)	19.0 (16.4; 22.1)
C	NIMENRIX	341	98.5% (96.6; 99.5)	196 (175; 219)
	MenC-CRM	116	81.9% (73.7; 88.4)	40.3 (29.5; 55.1)
W-135	NIMENRIX	336	87.5% (83.5 ; 90.8)	48.9 (41.2; 58.0)
Y	NIMENRIX	329	79.3% (74.5; 83.6)	30.9 (25.8; 37.1)

The analysis of immunogenicity was conducted on ATP cohort for immunogenicity.

(1) blood sampling performed 42 to 56 days post vaccination

* tested at GSK laboratories

N = number of subjects with available results

GMT = geometric mean antibody titre

In Study Men ACWY-TT-104, the immune response following one or two doses of NIMENRIX given 2 months apart was evaluated one month and 1 year after the last vaccination. NIMENRIX elicited bactericidal responses against all four groups that were similar in terms of % with rSBA titre ≥8 and GMT after one or two doses (Table 4).

Table 4: Bactericidal antibody responses (rSBA*) in toddlers aged 12-14 months

Meningo-coccal Group	Vaccine Group	Timing	Study MenACWY-TT-104[(1)]		
			N	≥8 (95% CI)	GMT (95% CI)
A	Nimenrix 1 dose	1 Month Post dose 1	180	97.8% (94.4; 99.4)	1437.0 (1118.3; 1846.6)
		1 Year Post dose 1	167	63.5% (55.7; 70.8)	62.7 (42.6; 92.2)
	Nimenrix 2 doses	1 Month Post dose 1	158	96.8% (92.8; 99.0)	1275.2 (970.5; 1675.4)
		1 Month Post dose 2	150	98.0% (94.3; 99.6)	1176.3 (921.8; 1501)
		1 Year Post dose 2	143	70.6% (62.4; 77.9)	76.6 (50.7; 115.7)
C	Nimenrix 1 dose	1 Month Post dose 1	179	95.0% (90.7; 97.7)	452.3 (345.6; 591.9)
		1 Year Post dose 1	167	49.1% (41.3; 56.9)	16.2 (12.4; 21.1)

Meningo-coccal Group	Vaccine Group	Timing	Study MenACWY-TT-104[(1)]		
			N	≥8 (95% CI)	GMT (95% CI)
	Nimenrix 2 doses	1 Month Post dose 1	157	95.5% (91.0; 98.2)	369.3 (280.9; 485.5)
		1 Month Post dose 2	150	98.7% (95.3; 99.8)	639.1 (521.8; 782.9)
		1 Year Post dose 2	143	55.2% (46.7; 63.6)	21.2 (15.6; 28.9)
W-135	Nimenrix 1 dose	1 Month Post dose 1	180	95.0% (90.8; 97.7)	2120.2 (1601.0; 2807.8)
		1 Year Post dose 1	167	65.3% (57.5; 72.5)	57.2 (39.9; 82.0)
W-135	Nimenrix 2 doses	1 Month Post dose 1	158	94.9% (90.3; 97.8)	2030.1 (1510.7; 2728.2)
		1 Month Post dose 2	150	100% (97.6; 100)	3533.0 (2914.5; 4282.7)
		1 Year Post dose 2	143	77.6% (69.9; 84.2)	123.1 (82.7; 183.4)
Y	Nimenrix 1 dose	1 Month Post dose 1	180	92.8% (88.0; 96.1)	951.8 (705.0; 1284.9)
		1 Year Post dose 1	167	73.1% (65.7; 79.6)	76.8 (54.2; 109.0)
	Nimenrix 2 doses	1 Month Post dose 1	157	93.6% (88.6; 96.9)	933.3 (692.3; 1258.3)
		1 Month Post dose 2	150	99.3% (96.3; 100)	1133.6 (944.5; 1360.5)
		1 Year Post dose 2	143	79.7% (72.2; 86.0)	112.3 (77.5; 162.8)

The analysis of immunogenicity was conducted on the according-to-protocol (ATP) cohort for immunogenicity
(1) blood sampling performed 21-48 days post vaccination and 44-60 weeks post vaccination
*tested at Public Health England laboratories

In the study MenACWY-TT-104, the serum bactericidal activity was also measured using hSBA as a secondary endpoint. In terms of % with hSBA titre ≥8, at one month post vaccination, responses against groups W-135 and Y were higher after two doses of NIMENRIX than after one dose, while responses against groups A and C were similar in the two groups. At one year post vaccination, the % responses with hSBA titre ≥1:8 for groups A, C, W-135 and Y were similar in both the one and two dose groups (Table 5).

Table 5: Bactericidal antibody responses (hSBA*) in toddlers aged 12-14 months

Meningococcal Group	Vaccines group	Timing	Study MenACWY-TT-104[(1)]		
			N	≥8 (95% CI)	GMT (95% CI)
A	Nimenrix 1 dose	1 Month Post dose 1	74	95.9% (88.6; 99.2)	118.0 (86.8; 160.5)
		1 Year Post dose 1	70	35.7% (24.6; 48.1)	6.1 (4.1; 8.9)
	Nimenrix 2 doses	1 Month Post dose 1	66	97.0% (89.5; 99.6)	132.9 (98.1; 180.1)
		1 Month Post dose 2	66	97.0% (89.5; 99.6)	170.5 (126.2; 230.2)
		1 Year Post dose 2	62	35.5% (23.7; 48.7)	6.4 (4.2; 10.0)
C	Nimenrix 1 dose	1 Month Post dose 1	78	98.7% (93.1; 100)	151.9 (104.8; 220.4)
	Nimenrix 1 dose	1 Year Post dose 1	71	80.3% (69.1; 88.8)	35.2 (22.5; 55.2)
C	Nimenrix 2 doses	1 Month Post dose 1	70	95.7% (88.0; 99.1)	160.8 (109.8; 235.5)
		1 Month Post dose 2	69	100% (94.8; 100)	1753.3 (1277.7; 2404.2)
		1 Year Post dose 2	63	90.5% (80.4; 96.4)	73.4 (47.5; 113.4)
W-135	Nimenrix 1 dose	1 Month Post dose 1	72	62.5% (50.3; 73.6)	27.5 (16.1; 46.8)
		1 Year Post dose 1	72	95.8% (88.3; 99.1)	209.0 (149.9; 291.4)
	Nimenrix 2 doses	1 Month Post dose 1	61	68.9% (55.7; 80.1)	26.2 (16.0; 43.0)
		1 Month Post dose 2	70	97.1% (90.1; 99.7)	756.8 (550.1; 1041.3)
		1 Year Post dose 2	65	98.5% (91.7; 100.0)	232.6 (168.3; 321.4)
Y	Nimenrix 1 dose	1 Month Post dose 1	71	67.6% (55.5; 78.20)	41.2 (23.7; 71.5)
		1 Year Post dose 1	62	91.9% (82.2; 97.3)	144.4 (97.2; 214.5)
	Nimenrix 2 doses	1 Month Post dose 1	56	64.3% (50.4; 76.6)	31.9 (17.6; 57.9)
		1 Month Post dose 2	64	95.3% (86.9; 99.0)	513.0 (339.4; 775.4)
		1 Year Post dose 2	58	87.9% (76.7; 95.0)	143.9 (88.5; 233.8)

The analysis of immunogenicity was conducted on the according-to-protocol (ATP) cohort for immunogenicity

(1) blood sampling performed 21-48 days post vaccination and 44-60 weeks post vaccination

*tested at GSK laboratories

Children

Immunogenicity in children aged 2-10 years

In two comparative studies of non-inferiority conducted in subjects aged 2-10 years, one dose of NIMENRIX was compared to either the licensed GlaxoSmithKline Biologicals' plain polysaccharide meningococcal groups A, C, W-135, Y (ACWY-PS) vaccine (study MenACWY-TT-038) or a licensed MenC-CRM vaccine (study MenACWY-TT-081).

In the MenACWY-TT-038 study, NIMENRIX was demonstrated to be non-inferior to the licensed ACWY-PS vaccine in terms of vaccine response to the four groups (A, C, W-135 and Y) (Table 6).

Table 6: Bactericidal antibody responses (rSBA*) to NIMENRIX compared with ACWY-PS vaccine in children aged 2-10 years one month after vaccination (study MenACWY-TT-038)

Group	NIMENRIX			ACWY-PS vaccine		
	N	VR (95%CI)	GMT (95%CI)	N	VR (95%CI)	GMT (95%CI)
A	594	89.1% (86.3 91.5)	6343 (5998; 6708)	192	64.6% (57.4; 71.3)	2283 (2023; 2577)
C	691	96.1% (94.4; 97.4)	4813 (4342; 5335)	234	89.7% (85.1; 93.3)	1317 (1043; 1663)
W-135	691	97.4% (95.9; 98.4)	11543 (10873; 12255)	236	82.6% (77.2; 87.2)	2158 (1815; 2565)
Y	723	92.7% (90.5; 94.5)	10825 (10233; 11452)	240	68.8% (62.5; 74.6)	2613 (2237; 3052)

The analysis of immunogenicity was conducted on ATP cohort for immunogenicity.

VR: vaccine response, defined as rSBA titres ≥ 32 for initially seronegative subjects or at least a 4-fold increase in rSBA titres from pre- to post-vaccination for initially seropositive subjects

*tested at GSK laboratories

N = number of subjects with available results

GMT = geometric mean antibody titre

In the MenACWY-TT-081 study, NIMENRIX (N=268) was demonstrated to be non-inferior to a licensed MenC-CRM vaccine (N=92) in 2 to 10 year olds in terms of group C vaccine response one month post-vaccination [94.8% (95% CI: 91.4; 97.1) and 95.7% (95% CI: 89.2; 98.8) respectively]. Group C geometric mean titres (GMTs) were lower for the NIMENRIX group [2795 (95% CI: 2393; 3263)] versus the MenC-CRM group [5292 (95% CI: 3815; 7340)].

Adolescents and Adults

Immunogenicity in adolescents aged 11-17 years and adults aged ≥ 18

In two clinical studies, one dose of NIMENRIX was compared to one dose of ACWY-PS vaccine administered to adolescents aged 11-17 years (study MenACWY-TT-036) and in adults aged 18-55 years (study MenACWY-TT-035).

In both adolescents and adults, NIMENRIX was demonstrated to be immunologically non-inferior to the ACWY-PS vaccine in terms of vaccine response. The antibody response to the four meningococcal groups elicited by NIMENRIX was either similar or higher than those elicited by the ACWY-PS vaccine (Table 7).

Table 7: Bactericidal antibody responses (rSBA*) to NIMENRIX compared with ACWY-PS vaccine in adolescents aged 11-17 years and adults aged 18-55 years one month after vaccination

Study (Age range)	Group	NIMENRIX			ACWY-PS vaccine		
		N	VR (95%CI)	GMT (95%CI)	N	VR (95%CI)	GMT (95%CI)
MenACWY-TT-036 (11-17 years)	A	553	85.4% (82.1; 88.2)	5928 (5557; 6324)	191	77.5% (70.9; 83.2)	2947 (2612; 3326)
	C	642	97.4% (95.8; 98.5)	13110 (11939; 14395)	211	96.7% (93.3; 98.7)	8222 (6807; 9930)
	W-135	639	96.4% (94.6; 97.7)	8247 (7639; 8903)	216	87.5% (82.3; 91.6)	2633 (2299; 3014)
	Y	657	93.8% (91.6; 95.5)	14086 (13168; 15069)	219	78.5% (72.5; 83.8)	5066 (4463; 5751)
MenACWY-TT-035 (18-55 years)	A	743	80.1% (77.0; 82.9)	3625 (3372; 3897)	252	69.8% (63.8; 75.4)	2127 (1909; 2370)
	C	849	91.5% (89.4; 93.3)	8866 (8011; 9812)	288	92.0% (88.3; 94.9)	7371 (6297; 8628)
	W-135	860	90.2% (88.1; 92.1)	5136 (4699; 5614)	283	85.5% (80.9; 89.4)	2461 (2081; 2911)
	Y	862	87.0% (84.6; 89.2)	7711 (7100; 8374)	288	78.8% (73.6; 83.4)	4314 (3782; 4921)

The analysis of immunogenicity was conducted on ATP cohorts for immunogenicity.

VR: vaccine response, defined as rSBA titres ≥ 32 for initially negative subjects or at least a 4-fold increase in rSBA titres from pre- to post-vaccination for initially positive subjects

* tested at GSK laboratories

N = number of subjects with available results

GMT = geometric mean antibody titre

In a separate study (MenACWY-TT-085) a single dose of NIMENRIX was administered to 194 Lebanese adults 56 years of age and older (including 133 aged 56-65 years and 61 aged > 65 years). The percentage of subjects with rSBA titres (measured at GSK's laboratories) ≥ 128 before vaccination ranged from 45% (group C) to 62% (group Y). Overall, at one month post-vaccination the percentage of vaccines with rSBA titres ≥ 128 ranged from 93% (group C) to 97% (group Y). In the subgroup aged > 65 years the percentage of vaccines with

rSBA titres ≥ 128 at one month post-vaccination ranged from 90% (group A) to 97% (group Y).

Persistence of immune response

Toddlers

Persistence of immune response in toddlers aged 12-23 months at vaccination

In study MenACWY-TT-048, the persistence of the immune response was evaluated by rSBA and hSBA up to 4 years after vaccination in toddlers primed in study MenACWY-TT-039 (Table 8) and up to 5 years in study MenACWY-TT-032 (Table 9).

Table 8: Four year persistence data in toddlers aged 12-23 months at vaccination

Group	Response to	Time-point (Years)	rSBA*			hSBA**		
			N	≥8 (95%CI)	GMT (95%CI)	N	≥8 (95%CI)	GMT (95%CI)
A	NIMENRIX	3	262	59.9% (53.7; 65.9)	19.3 (15.7; 23.6)	251	35.9% (29.9; 42.1)	5.8 (4.8; 7.0)
		4	224	74.1% (67.9; 79.7)	107 (77.6; 148)	198	28.8% (22.6; 35.6)	4.9 (4.0; 6.0)
C	NIMENRIX	3	262	35.9% (30.1; 42.0)	9.8 (8.1; 11.7)	253	78.3% (72.7; 83.2)	37.8 (29.4; 48.6)
		4	225	40.4% (34.0; 47.2)	12.3 (9.8; 15.3)	209	73.2% (66.7; 79.1)	32.0 (23.8; 43.0)
	MenC-CRM vaccine	3	46	13.0% (4.9; 26.3)	5.7 (4.2; 7.7)	31	41.9% (24.5; 60.9)	6.2 (3.7; 10.3)
		4	45	35.6% (21.9; 51.2)	13.5 (7.4; 24.5)	32	46.9% (29.1; 65.3)	11.3 (4.9; 25.6)
W-135	NIMENRIX	3	261	49.8% (43.6; 56.0)	24.9 (19.2; 32.4)	254	82.3% (77.0; 86.8)	52.0 (41.4; 65.2)
		4	225	49.3% (42.6; 56.1)	30.5 (22.4; 41.5)	165	80.6% (73.7; 86.3)	47.1 (35.7; 62.2)
Y	NIMENRIX	3	262	53.8% (47.6; 60.0)	22.3 (17.6; 28.4)	250	72.0% (66.0; 77.5)	33.2 (25.9; 42.5)
		4	225	58.2% (51.5; 64.7)	36.2 (27.1; 48.4)	130	65.4% (56.5; 73.5)	29.8 (20.2; 44.1)

The analysis of immunogenicity was conducted on ATP cohort for persistence adapted for each time-point.

*rSBA testing performed at PHE laboratories in UK

** tested at GSK laboratories

Table 9: 5 years persistence data in toddlers aged 12-23 months at vaccination

Group	Response to	Time-point (Years)	rSBA*			hSBA**		
			N	≥8 (95%CI)	GMT (95%CI)	N	≥8 (95%CI)	GMT (95%CI)
A	NIMENRIX	4	45	64.4% (48.8; 78.1)	35.1 (19.4; 63.4)	44	52.3% (36.7; 67.5)	8.8 (5.4; 14.2)
		5	49	73.5% (58.9; 85.1)	37.4 (22.1; 63.2)	45	35.6% (21.9; 51.2)	5.2 (3.4; 7.8)
C	NIMENRIX	4	45	97.8% (88.2; 99.9)	110 (62.7; 192)	45	97.8% (88.2; 99.9)	370 (214; 640)
		5	49	77.6% (63.4; 88.2)	48.9 (28.5; 84.0)	48	91.7% (80.0; 97.7)	216 (124; 379)
	MenC-CRM vaccine	4	10	80.0% (44.4; 97.5)	137 (22.6; 832)	10	70.0% (34.8; 93.3)	91.9 (9.8; 859)
		5	11	63.6% (30.8; 89.1)	26.5 (6.5; 107)	11	90.9% (58.7; 99.8)	109 (21.2; 557)
W-135	NIMENRIX	4	45	60.0% (44.3; 74.3)	50.8 (24.0; 108)	45	84.4% (70.5; 93.5)	76.9 (44.0; 134)
		5	49	34.7% (21.7; 49.6)	18.2 (9.3; 35.3)	46	82.6% (68.6; 92.2)	59.7 (35.1; 101)
Y	NIMENRIX	4	45	62.2% (46.5; 76.2)	44.9 (22.6; 89.3)	41	87.8% (73.8; 95.9)	74.6 (44.5; 125)
		5	49	42.9% (28.8; 57.8)	20.6 (10.9; 39.2)	45	80.0% (65.4; 90.4)	70.6 (38.7; 129)

Persistence of immunogenicity was analysed using the year 5 ATP cohort.

*rSBA testing performed at PHE laboratories in UK

** tested at GSK laboratories

Children

Persistence of immune response in children aged 2-10 years

In study MenACWY-TT-088, the persistence of the immune response was evaluated by rSBA up to 68 months after vaccination in children 2-10 years of age primed in study MenACWY-TT-081 (Table 10).

Table 10: 68 months persistence data in children 2-10 years of age at vaccination

Group	Response to	Time-point (months)	rSBA*			hSBA**		
			N	≥8 (95%CI)	GMT (95%CI)	N***	≥8 (95%CI)	GMT (95%CI)
A	NIMENRIX	32	193	86.5% (80.9; 91.0)	196 (144; 267)	90	25.6% (16.9; 35.8)	4.6 (3.3; 6.3)
		68	178	86.5% (80.6; 91.2)	129 (93.5; 179)	170	40.6% (33.1; 48.4)	6.9 (5.4; 8.9)
C	NIMENRIX	32	192	64.6% (57.4; 71.3)	34.8 (26.0; 46.4)	90	95.6% (89.0; 98.8)	75.9 (53.4; 108)
		68	178	39.9% (32.6; 47.5)	14.2 (10.8; 18.7)	172	75.6% (68.5; 81.8)	28.4 (21.2; 37.9)
	MenC-CRM vaccine	32	69	76.8% (65.1; 86.1)	86.5 (47.3; 158)	33	90.9% (75.7; 98.1)	82.2 (34.6; 196)

Group	Response to	Time-point (months)	rSBA*			hSBA**		
			N	≥8 (95%CI)	GMT (95%CI)	N***	≥8 (95%CI)	GMT (95%CI)
		68	61	62.3% (49.0; 74.4)	44.5 (23.7; 83.6)	57	75.4% (62.2; 85.9)	34.3 (19.0; 61.9)
W-135	NIMENRIX	32	193	77.2% (70.6; 82.9)	214 (149; 307)	86	84.9% (75.5; 91.7)	69.9 (48.2; 101)
		68	178	52.8% (45.2; 60.3)	59.2 (39.3; 89.2)	159	78.6% (71.4; 84.7)	56.7 (41.5; 77.3)
Y	NIMENRIX	32	193	81.3% (75.1; 86.6)	227 (165; 314)	91	81.3% (71.8; 88.7)	79.2 (52.5; 119)
		68	178	71.3% (64.1; 77.9)	139 (96.0; 202)	159	73.0% (65.3; 79.7)	56.3 (39.5; 80.3)

The analysis of immunogenicity was conducted on ATP cohort for persistence adapted for each time-point.

*rSBA testing performed at PHE laboratories in UK

** tested at GSK laboratories

*** at month 32, a subset of subjects have been tested for hSBA

Persistence of immune response in children aged 6-10 years at vaccination

In study MenACWY-TT-028, the persistence of the immune response was evaluated by hSBA one year after vaccination in children primed at 6-10 years of age with either NIMENRIX or ACWY-PS vaccine in study MenACWY-TT-027 (Table 11).

Table 11: 1 month post-vaccination and 1 year persistence data (hSBA*) in children 6-10 years of age at vaccination

Group	Response to	1 month post-vaccination			1 year persistence		
		N	≥8 (95%CI)	GMT (95%CI)	N	≥8 (95%CI)	GMT (95%CI)
A	NIMENRIX	105	80.0 % (71.1; 87.2)	53.4 (37.3; 76.2)	104	16.3% (9.8; 24.9)	3.5 (2.7; 4.4)
	ACWY-PS	35	25.7% (12.5;43.3)	4.1 (2.6;6.5)	35	5.7% (0.7;19.2)	2.5 (1.9;3.3)
C	NIMENRIX	101	89.1% (81.3;94.4)	155.8 (99.3;244)	105	95.2% (89.2;98.4)	129.5 (95.4;176)
	ACWY-PS	38	39.5% (24.0;56.6)	13.1 (5.4;32.0)	31	32.3% (16.7;51.4)	7.7 (3.5;17.3)
W-135	NIMENRIX	103	95.1% (89.0;98.4)	133.5 (99.9;178)	103	100% (96.5;100)	256.7 (218.2;302)
	ACWY-PS	35	34.3% (19.1;52.2)	5.8 (3.3;9.9)	31	12.9% (3.6;29.8)	3.4 (2.0;5.8)
Y	NIMENRIX	89	83.1% (73.7;90.2)	95.1 (62.4;145.1)	106	99.1% (94.9;100)	265.0 (213;330)
	ACWY-PS	32	43.8% (26.4;62.3)	12.5 (5.6;27.7)	36	33.3% (18.6;51.0)	9.3 (4.3;19.9)

The analysis of immunogenicity was conducted on ATP cohort for persistence.

*tested at GSK Laboratories

Adolescents and Adults

Persistence of immune response in adolescents aged 11-17 years at vaccination

In study MenACWY-TT-043, the persistence of the immune response was evaluated up to 5 years after vaccination in adolescents primed with either NIMENRIX or ACWY-PS vaccine in study MenACWY-TT-036 (Table12). See Table 4-7 for the primary vaccination results from study MenACWY-TT-036.

Table 12: 5 year persistence data in adolescents aged 11-17 years at vaccination

Group	Time-point (Years)	NIMENRIX			ACWY-PS vaccine		
		N	≥8 (95%CI)	GMT (95%CI)	N	≥8 (95%CI)	GMT (95%CI)
A	3	449	92.9% (90.1; 95.1)	448 (381; 527)	150	82.7% (75.6; 88.4)	206 (147; 288)
	5	236	97.5 % (94.5; 99.1)	644 (531; 781)	86	93.0 (85.4; 97.4)	296 (202; 433)
C	3	449	91.1% (88.1; 93.6)	371 (309; 446)	150	86.0% (79.4; 91.1)	390 (262; 580)
	5	236	88.6 % (83.8; 92.3)	249 (194; 318)	85	87.1 (78.0; 93.4)	366 (224; 599)
W-135	3	449	82.0% (78.1; 85.4)	338 (268; 426)	150	30.0% (22.8; 38.0)	16.0 (10.9; 23.6)
	5	236	86.0% (80.9; 90.2)	437 (324; 588)	86	34.9 (24.9; 45.9)	19.7 (11.8; 32.9)
Y	3	449	93.1% (90.3; 95.3)	740 (620; 884)	150	58.0% (49.7; 66.0)	69.6 (44.6; 109)
	5	236	96.6% (93.4; 98.5)	1000 (824; 1214)	86	66.3 (55.3; 76.1)	125 (71.2; 219)

The analysis of immunogenicity was conducted on ATP cohort for persistence adapted for each time point.
*rSBA testing performed at PHE laboratories in UK

Persistence of immune response in adolescents and adults aged 11-25 years at vaccination

In study MenACWY-TT-059, the persistence of the immune response was evaluated by hSBA up to 5 years after vaccination in adolescents and adults 11-25 years of age primed in study MenACWY-TT-052. For all groups (A, C, W-135, Y), the persistence of antibodies elicited by NIMENRIX was similar or higher than those induced by the licensed quadrivalent meningococcal diphtheria toxoid (DT) conjugate vaccine (ACWY-DT) (Table 13).

Table 13: 1 month post-vaccination and 5 years persistence data in adolescents and adults 11-25 years of age at vaccination

Group	Response to	Time-point	N	≥8 (95%CI)	GMT (95%CI)
A	NIMENRIX	Month 1	356	82.0% (77.6; 85.9)	58.7 (48.6; 70.9)
		Year 1	350	29.1% (24.4; 34.2)	5.4 (4.5; 6.4)
		Year 5	141	48.9 % (40.4; 57.5)	8.9 (6.8; 11.8)
	ACWY-DT	Month 1	107	73.8% (64.4; 81.9)	42.5 (28.5; 63.3)
		Year 1	111	31.5% (23.0; 41.0)	6.0 (4.3; 8.5)
		Year 5	45	44.4% (29.6; 60.0)	7.9 (4.8; 13.2)
C	NIMENRIX	Month 1	359	96.1% (93.5; 97.9)	532 (424; 668)
		Year 1	336	94.9% (92.0; 97.0)	172 (142; 207)
		Year 5	140	92.9% (87.3; 96.5)	94.6 (65.9; 136)
	ACWY-DT	Month 1	113	99.1% (95.2; 100)	317 (217; 462)
		Year 1	105	73.3% (63.8; 81.5)	46.7 (30.2; 72.1)
		Year 5	44	79.5% (64.7; 90.2)	30.6 (17.3; 54.4)
W-135	NIMENRIX	Month 1	334	91.0% (87.4; 93.9)	117 (96.8; 141)
		Year 1	327	98.5% (96.5; 99.5)	197 (173; 225)
		Year 5	138	87.0% (80.2; 92.1)	103 (76.3; 140)
	ACWY-DT	Month 1	96	75.0% (65.1; 83.3)	70.4 (43.7; 113)
		Year 1	107	75.7% (66.5; 83.5)	48.9 (32.5; 73.8)
		Year 5	44	84.1% (69.9; 93.4)	70.4 (37.2; 133)
Y	NIMENRIX	Month 1	364	95.1% (92.3; 97.0)	246 (208; 291)
		Year 1	356	97.8% (95.6; 99.0)	272 (237; 311)
		Year 5	142	94.4% (89.2; 97.5)	225 (174; 290)
	ACWY-DT	Month 1	111	81.1% (72.5; 87.9)	103 (67.5; 159)
		Year 1	112	86.6% (78.9; 92.3)	101 (69.6; 146)
		Year 5	44	90.9% (78.3; 97.5)	129 (77.4; 216)

The analysis of immunogenicity was conducted on ATP cohort for persistence adapted for each time-point.
* tested at GSK laboratories

Immune memory

In study MenACWY-TT-014, the induction of immune memory was assessed one month after the administration of a one fifth dose of ACWY-PS vaccine (10 µg of each polysaccharide) to children in the third year of life. These children were previously primed in study MenACWY-TT-013 with either NIMENRIX or a licensed MenC-CRM vaccine at the age of 12 to 14 months.

One month after the challenge dose, the GMTs elicited by the subjects primed with NIMENRIX increased 6.5 to 8-fold, indicating that NIMENRIX induces immune memory to all four groups A, C, W-135 and Y. The post-challenge rSBA-MenC GMT was similar in both study groups, indicating that NIMENRIX induces an analogous immune memory to group C as the licensed MenC-CRM vaccine (Table 14).

Table 14: Immune response (rSBA*) 1 month after a challenge vaccination in subjects primed with NIMENRIX or a MenC-CRM vaccine at the age of 12 to 14 months

Group	Response to	Pre-challenge		Post-challenge	
		N	rSBA GMT (95%CI)	N	rSBA GMT (95%CI)
A	NIMENRIX	32	544 (325; 911)	25	3322 (2294 4810)
C	NIMENRIX	31	174 (105; 289)	32	5966 (4128; 8621)
	MenC-CRM	28	34.4 (15.8; 75.3)	30	5265 (3437; 8065.1)
W-135	NIMENRIX	32	644 (394; 1052)	32	11058 (8587; 14240)
Y	NIMENRIX	32	440 (274; 706)	32	5737 (4216; 7806)

The analysis of immunogenicity was conducted on ATP cohort for immunogenicity.

* tested at GSK laboratories

NIMENRIX booster vaccination after priming in toddlers, children, adolescents and adults

For subjects primed with NIMENRIX aged 1 year and above and boosted with NIMENRIX 4 or 5 years later, more than 99.0% of all subjects achieved post-booster SBA titres ≥ 1:8 for both assays (studies MenACWY-TT-062, 048, 059, 088). One month after the booster vaccination, the GMTs elicited were significantly higher than those elicited by age matched naïve control groups, indicating that NIMENRIX induces immune memory to groups A, C, W-135, and Y.

The observed MenC booster response with NIMENRIX was similar to that observed in subjects primed and boosted with a monovalent MenC-CRM conjugate vaccine (study MenACWY-TT-048). One year after NIMENRIX booster, SBA titres ≥ 1:8 persisted in at least 95.5% of subjects (study MenACWY-TT-048, 12 to 23 months of age at primary vaccination).

When NIMENRIX was used as a booster following primary vaccination with a MenACWY-DT conjugate vaccine or a monovalent MenC conjugate vaccine (study MenACWY-TT-059, 10 to 25 years of age at primary vaccination and study MenACWY-TT-088, 2 to 10 years of age at primary vaccination), the titres increased by 48-340 fold for all groups and 100% of the subjects reached SBA titres ≥ 1:8.

Immunogenicity in subjects previously vaccinated with a plain polysaccharide meningococcal vaccine

In study MenACWY-TT-021 conducted in subjects aged 4.5-34 years, the immunogenicity of NIMENRIX administered between 30 and 42 months after vaccination with an ACWY-PS vaccine was compared to the immunogenicity of NIMENRIX administered to age-matched subjects who had not been vaccinated with any meningococcal vaccine in the preceding 10 years. The rSBA GMTs were significantly lower in the subjects who had

received a dose of ACWY-PS vaccine 30-42 months prior to NIMENRIX (Table 15). Clinical relevance of this observation is unknown since all subjects achieved rSBA titres ≥ 8 for each group (A, C, W-135, Y) regardless of meningococcal vaccination history.

Table 15: Immune response (rSBA*) one month after NIMENRIX vaccination in subjects according to their meningococcal vaccine history

Group	Subjects vaccinated 30 to 42 months previously with ACWY-PS			Subjects who had not received a meningococcal vaccine in the preceding 10 years		
	N	rSBA ≥8 (95%CI)	GMT (95%CI)	N	rSBA ≥8 (95%CI)	GMT (95%CI)
A	146	100% (97.5; 100)	6868.8 (6045; 7805)	69	100% (94.8; 100)	13015 (10722; 15798)
C	169	100% (97.8; 100)	1946 (1583.3; 2391.1)	75	100% (95.2; 100)	5495 (4266; 7076)
W-135	169	100% (97.8; 100)	4636 (3942; 5451)	75	100% (95.2; 100)	9078 (7088; 11627)
Y	169	100% (97.8; 100)	77800 (6683; 9104)	75	100% (95.2; 100)	13895 (11186; 17261)

The analysis of immunogenicity was conducted on ATP cohort for immunogenicity.

* tested at GSK

Response to NIMENRIX in subjects at increased risk for meningococcal infections

Study MenACWY-TT-084 evaluated the immunogenicity of 1 and 2 doses of NIMENRIX given two months apart in 43 at-risk subjects aged 2-17 years (at increased risk for meningococcal disease, i.e., asplenic subjects, and hyposplenic subjects) compared to 43 healthy age-matched subjects.

One month after the first vaccine dose, vaccine response rates (rSBA titre ≥1:32 or a ≥4-fold increase in rSBA titre from baseline) for groups A, C, W, and Y, respectively, were 100%, 92.5%, 100% and 97.5% in the at-risk group and were 97.5%, 97.5%, 97.5%, and 100% for healthy subjects. After the second vaccine dose, vaccine response rates in both at-risk and healthy subjects were 100% for each of the 4 meningococcal groups.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on local tolerance, acute toxicity, repeated dose toxicity, developmental/reproductive toxicity and fertility studies.

Genotoxicity

No data available.

Carcinogenicity

The carcinogenic potential of NIMENRIX has not been investigated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Sucrose
Trometamol

Solvent:
0.9% Sodium chloride
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

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. .

After reconstitution:

After reconstitution, the vaccine should be used immediately. For shelf-life after reconstitution of the medicinal product, see Section 4.2 Use and handling.

6.4 Special precautions for storage

NIMENRIX must be stored between +2°C to +8°C. The sterile 0.9% saline diluent may be refrigerated or stored at ambient temperatures, but must not be frozen. The vaccine should be stored in the original package in order to protect from light.

6.5 Nature and contents of container

NIMENRIX is supplied in a single dose as a white lyophilised powder in a glass vial (type 1 glass) with a stopper (butyl rubber), together with 0.5mL solvent either in a glass ampoule (type I glass) or a pre-filled syringe with a stopper (butyl rubber).

Pack sizes of 1 and 10 without separate needles.

Not all pack sizes or presentations may be marketed.

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

No data available.

CAS number

No data available.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8 SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9 DATE OF FIRST APPROVAL

29 August 2013

10 DATE OF REVISION

11 February 2020

Summary Table of Changes

Section changed	Summary of new information
4.4	Amendment of information pertaining to special populations; consideration of a second dose for toddlers at risk.
4.5	Concomitant use with HPV2 and Tdap.
4.8	Co-administration with HPV2 and Tdap.
5.1	Response in subjects at increased risk.
6.3	Direction to ARTG for shelf-life details.
8	Change in Sponsor address.

® Registered Trademark

NIMENRIX® is a registered trademark of GlaxoSmithKline Biologicals SA, licensed to Pfizer Inc