ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nimenrix powder and solvent for solution for injection in pre-filled syringe
Meningococcal group A, C, W-135 and Y conjugate vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (0.5 ml) contains:

Neisseria meningitidis group A polysaccharide[1]	5 micrograms
Neisseria meningitidis group C polysaccharide[1]	5 micrograms
Neisseria meningitidis group W-135 polysaccharide[1]	5 micrograms
Neisseria meningitidis group Y polysaccharide[1]	5 micrograms
[1]conjugated to tetanus toxoid carrier protein	44 micrograms

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
The powder or cake is white.
The solvent is clear and colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Nimenrix should be used in accordance with available official recommendations.

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).

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).

Previously vaccinated children from 12 months of age, adolescents and adults
Nimenrix may be given as a booster dose in individuals who have previously received primary vaccination with a conjugated or plain polysaccharide meningococcal vaccine (see sections 4.4 and 5.1).

Method of administration

Immunisation should be carried out by intramuscular injection only.

In infants, the recommended injection site is the anterolateral aspect of the thigh. In individuals from 1 year of age, the recommended injection site is the anterolateral aspect of the thigh or the deltoid muscle (see sections 4.4 and 4.5).

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

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.

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

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 especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

Thrombocytopenia and coagulation disorders

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.

Safety and immunogenicity have not been assessed in patients with increased susceptibility to meningococcal infection due to conditions such as terminal complement deficiencies and anatomic or functional asplenia. In these individuals, an adequate immune response may not be elicited.

Protection against meningococcal disease

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

A protective immune response may not be elicited in all vaccinees.

Effect of prior vaccination with plain polysaccharide meningococcal vaccine
Subjects previously vaccinated with a plain polysaccharide meningococcal vaccine and vaccinated with Nimenrix 30 to 42 months later had lower Geometric Mean Titres (GMTs) measured with rabbit complement serum bactericidal assay (rSBA) than subjects who had not been vaccinated with any meningococcal vaccine in the preceding 10 years (see section 5.1). The clinical relevance of this observation is unknown.

Effect of pre-vaccination antibody to tetanus toxoid
The safety and immunogenicity of Nimenrix was evaluated when it was sequentially administered or co-administered with a vaccine containing, diphtheria and tetanus toxoids, acellular pertussis, inactivated polioviruses (1, 2 and 3), hepatitis B surface antigen and *Haemophilus influenzae* type b polyribosyl ribose phosphate conjugated to tetanus toxoid (DTaP-HBV-IPV/Hib) in the second year of life. The administration of Nimenrix one month after the DTaP-HBV-IPV/Hib vaccine resulted in lower rSBA GMTs against groups A, C and W-135 compared with co-administration (see section 4.5). The clinical relevance of this observation is unknown.

Immune responses in toddlers aged 12-14 months
Toddlers aged 12-14 months had similar rSBA responses to groups A, C, W-135 and Y at one month after one dose of Nimenrix or at one month after two doses of Nimenrix given two months apart.

A single dose was associated with lower human complement serum bactericidal assay (hSBA) titres to groups W-135 and Y compared with two doses given two months apart. Similar responses to groups A and C were observed after one or two doses (see section 5.1). The clinical relevance of the findings is unknown. If a toddler is expected to be at particular risk of invasive meningococcal disease due to exposure to groups W-135 and Y, consideration may be given to administering a second dose of Nimenrix after an interval of 2 months. Regarding waning of antibody against group A or group C 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

Following administration of Nimenrix there is a waning of serum bactericidal antibody titres against group A when using human complement in the assay (hSBA) (see section 5.1). The clinical relevance of the waning of hSBA antibody titres against group A is unknown. However, if an individual is expected to be at particular risk of exposure to group A and received a dose of Nimenrix more than approximately one year previously, consideration may be given to administering a booster dose.

A decline in antibody titres over time has been observed for groups A, C, W-135 and Y. 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 or Y (see section 5.1).

Effect of Nimenrix on anti-tetanus antibody concentrations

Although an increase of the anti-tetanus toxoid (TT) antibody concentrations was observed following vaccination with Nimenrix, Nimenrix does not substitute for tetanus immunisation.

Giving Nimenrix with or one month before a TT-containing vaccine in the second year of life does not impair the response to TT or significantly affect safety. No data are available beyond the age of 2 years.

4.5 Interaction with other medicinal products and other forms of interaction

In infants, Nimenrix can be given concomitantly with combined DTaP-HBV-IPV/Hib vaccines and with 10-valent pneumococcal conjugate vaccine.

From age 1 year 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.

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

Whenever possible, Nimenrix and a TT containing vaccine, such as DTaP-HBV-IPV/Hib vaccine, should 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). The clinical relevance of this observation is unknown. There was no impact of co-administration on immune responses to the other nine pneumococcal serotypes.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

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

Breast-feeding

It is unknown whether Nimenrix is excreted in human milk.

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

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

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. However, some of the effects mentioned under section 4.8 “Undesirable effects” may affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of Nimenrix has been evaluated in clinical studies as follows:

- A single dose was administered to 9,621 subjects. 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.
- In a study in infants aged 6 to 12 weeks at the time of the first dose, 1052 subjects received at least one dose of a primary series of 2 or 3 doses of Nimenrix and 1008 received a booster dose at approximately 12 months of age.

In the 6-12 weeks and in the 12-14 months age groups who received 2 doses of Nimenrix given 2 months apart, the first and second doses were associated with similar local and systemic reactogenicity.

The local and general adverse reaction profile of a booster dose of Nimenrix after primary vaccination with Nimenrix or other conjugated or plain polysaccharide meningococcal vaccines, was similar to the local and general adverse reaction profile observed after primary vaccination with Nimenrix, except for gastrointestinal symptoms (including diarrhoea, vomiting, and nausea), which were very common.

Tabulated list of adverse reactions

Adverse reactions reported are listed according to the following frequency categories:

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)

Table 1 shows the adverse reactions reported from the studies in subjects aged from 6 weeks up to 55 years of age and post-marketing experience. Adverse reactions reported in subjects aged >55 years were similar to those observed in younger adults.

Table 1 Tabulated summary of adverse reactions by system organ class		
System Organ Class	**Frequency**	**Adverse reactions**
Metabolism and nutrition disorders	Very common	Appetite lost
Psychiatric disorders	Very common	Irritability
	Uncommon	Insomnia Crying
Nervous system disorders	Very common	Drowsiness Headache
	Uncommon	Hypoaesthesia Dizziness
Gastrointestinal disorders	Common	Diarrhoea Vomiting Nausea*
Skin and subcutaneous tissue disorders	Uncommon	Pruritus Rash**
Musculoskeletal and connective tissue disorders	Uncommon	Myalgia Pain in extremity
General disorders and administration site conditions	Very common	Fever Swelling at injection site Pain at injection site Redness at injection site Fatigue
	Common	Injection site haematoma*
	Uncommon	Malaise Injection site induration Injection site pruritus Injection site warmth Injection site anaesthesia
	Unknown***	Extensive limb swelling at the injection site, frequently associated with erythema, sometimes involving the adjacent joint or swelling of the entire injected limb

*Nausea and Injection site haematoma occurred at a frequency of Uncommon in infants
**Rash occurred at a frequency of Common in infants
***ADR identified post-marketing

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, meningococcal vaccines, ATC code: J07AH08

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 *Neisseria meningitidis* group A, C, W-135 and Y when measured by assays using either rabbit complement (rSBA) or human complement (hSBA).

Immunogenicity in infants

In the clinical study in infants (MenACWY-TT-083), the first dose was administered at 6 to 12 weeks of age, the second dose was given after an interval of 2 months and a third (booster) dose was given at the age of approximately 12 months. DTaP-HBV-IPV/Hib and a 10-valent pneumococcal vaccine were co-administered. Nimenrix elicited a bactericidal antibody response against the four meningococcal groups. The response against group C was non-inferior to the one elicited by licensed MenC-CRM and MenC-TT vaccines in terms of percentages with rSBA titres ≥8 at one month after the second dose. See Table 2.

Table 2: Bactericidal antibody responses (rSBA*) and (hSBA) in infants after two doses given 2 months apart and after a booster dose at 12 months of age (Study MenACWY-TT-083)**

Meningococcal Group	Vaccine group		rSBA*			hSBA**		
			N	≥8 (95% CI)	GMT (95% CI)	N	≥8 (95% CI)	GMT (95% CI)
A	Nimenrix	Post dose 2[(1)]	456	97.4% (95.4; 98.6)	203 (182; 227)	202	96.5% (93.0; 98.6)	157 (131; 188)
		Post booster[(1)]	462	99.6% (98.4; 99.9)	1561 (1412; 1725)	214	99.5% (97.4;100)	1007 (836;1214)
C	Nimenrix	Post dose 2[(1)]	456	98.7% (97.2; 99.5)	612 (540; 693)	218	98.6% (96.0; 99.7)	1308 (1052; 1627)
		Post booster[(1)]	463	99.8% (98.8; 100)	1177 (1059; 1308)	221	99.5% (97.5; 100)	4992 (4086; 6100)
	MenC-CRM vaccine	Post dose 2[(1)]	455	99.6% (98.4; 99.9)	958 (850; 1079)	202	100% (98.2; 100)	3188 (2646; 3841)
		Post booster[(1)]	446	98.4% (96.8; 99.4)	1051 (920; 1202)	216	100% (98.3; 100)	5438 (4412; 6702)
	MenC-TT vaccine	Post dose 2[(1)]	457	100% (99.2; 100)	1188 (1080; 1307)	226	100% (98.4; 100)	2626 (2219; 3109)
		Post booster[(1)]	459	100% (99.2; 100)	1960 (1776; 2163)	219	100% (98.3; 100)	5542 (4765; 6446)
W	Nimenrix	Post dose 2[(1)]	455	99.1% (97.8; 99.8)	1605 (1383; 1862)	217	100% (98.3; 100)	753 (644; 882)
		Post booster[(1)]	462	99.8% (98.8; 100)	2777 (2485; 3104)	218	100% (98.3; 100)	5123 (4504; 5826)
Y	Nimenrix	Post dose 2[(1)]	456	98.2% (96.6; 99.2)	483 (419; 558)	214	97.7% (94.6; 99.2)	328 (276; 390)
		Post booster[(1)]	462	99.4% (99.1; 99.9)	881 (787; 986)	217	100% (98.3; 100)	2954 (2498; 3493)

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

[(1)] blood sampling performed 21 to 48 days post vaccination

Immunogenicity in toddlers aged 12-23 months

In clinical studies MenACWY-TT-039 and MenACWY-TT-040 a single dose of Nimenrix elicited rSBA responses against the four meningococcal groups, with a response against group C that was

comparable to the one elicited by the licensed MenC-CRM vaccine in terms of percentages with rSBA titres ≥8 (Table 3).

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

Meningococcal Group	Vaccine group	Study MenACWY-TT-039[(1)]			Study MenACWY-TT-040[(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 vaccine	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 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

In study MenACWY-TT-039, serum bactericidal activity was also measured using human serum as the source of complement (hSBA) as a secondary endpoint (Table 4).

Table 4: Bactericidal antibody responses (hSBA*) in toddlers aged 12-23 months

Meningococcal Group	Vaccine group	N	Study MenACWY-TT-039[(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 vaccine	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

In Study Men ACWY-TT-104 the immune response following one or two doses of Nimenrix given 2 months apart was evaluated one month 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 5).

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

Meningococcal Group	Vaccine group	Timing	Study MenACWY-TT-104[(1)]		
			N	≥8 (95%CI)	GMT (95% CI)
A	Nimenrix 1 dose	Post dose 1	180	97.8% (94.4, 99.4)	1437 (1118, 1847)
	Nimenrix 2 doses	Post dose 1	158	96.8% (92.8, 99.0)	1275 (970, 1675)
		Post dose 2	150	98.0% (94.3, 99.6)	1176 (922, 1501)
C	Nimenrix 1 dose	Post dose 1	179	95.0% (90.7, 97.7)	452 (346, 592)
	Nimenrix 2 doses	Post dose 1	157	95.5% (91.0, 98.2)	369 (281, 485)
		Post dose 2	150	98.7% (95.3, 99.8)	639 (522, 783)
W-135	Nimenrix 1 dose	Post dose 1	180	95.0% (90.8, 97.7)	2120 (1601, 2808)
	Nimenrix 2 doses	Post dose 1	158	94.9% (90.3, 97.8)	2030 (1511, 2728)
		Post dose 2	150	100% (97.6, 100)	3533 (2914, 4283)
Y	Nimenrix 1 dose	Post dose 1	180	92.8% (88.0, 96.1)	952 (705, 1285)
	Nimenrix 2 doses	Post dose 1	157	93.6% (88.6, 96.9)	933 (692, 1258)
		Post dose 2	150	99.3% (96.3, 100)	1134 (944, 1360)

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

[(1)] blood sampling performed 21-48 days post vaccination

* tested at Public Health England laboratories

In study MenACWY-TT-104, serum bactericidal activity was also measured using hSBA as a secondary endpoint. Nimenrix elicited bactericidal responses against groups W-135 and Y that were higher in terms of % with hSBA titre ≥8 when two doses were given compared with one. Similar responses in terms of % with hSBA titre ≥8 were observed with groups A and C (Table 6).

Table 6: Bactericidal antibody responses (hSBA)* in toddlers aged 12-14 months

Meningococcal Group	Vaccine group	Timing	Study MenACWY-TT-104[(1)]		
			N	≥8 (95%CI)	GMT (95% CI)
A	Nimenrix 1 dose	Post dose 1	74	95.9% (88.6, 99.2)	118 (87, 160)
	Nimenrix 2 doses	Post dose 1	66	97.0% (89.5, 99.6)	133 (98, 180)
		Post dose 2	66	97.0% (89.5, 99.6)	170 (126, 230)
C	Nimenrix 1 dose	Post dose 1	78	98.7% (93.1, 100)	152 (105, 220)
	Nimenrix 2 doses	Post dose 1	70	95.7% (88.0, 99.1)	161 (110, 236)
		Post dose 2	69	100% (94.8, 100)	1753 (1278, 2404)
W-135	Nimenrix 1 dose	Post dose 1	72	62.5% (50.3, 73.6)	27 (16, 47)
	Nimenrix 2 doses	Post dose 1	61	68.9% (55.7, 80.1)	26 (16, 43)
		Post dose 2	70	97.1% (90.1, 99.7)	757 (550, 1041)
Y	Nimenrix 1 dose	Post dose 1	71	67.6% (55.5, 78.20)	41 (24, 71)
	Nimenrix 2 doses	Post dose 1	56	64.3% (50.4, 76.6)	32 (18, 58)
		Post dose 2	64	95.3% (86.9, 99.0)	513 (339, 775)

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

[(1)] blood sampling performed 21-48 days post vaccination

*tested at GSK laboratories

Persistence of the immune response was evaluated by rSBA and hSBA up to 5 years in children initially vaccinated in study MenACWY-TT-027 (Table 7).

Table 7: 5 years persistence data in toddlers aged 12-23 months at vaccination (study MenACWY-TT-032; extension of study 027)

Meningococcal Group	Vaccine Group	Time-point (year)	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. A selection bias mainly due to revaccination of subjects with group C rSBA titres <8 and their exclusion from subsequent time-point(s) may have led to an overestimation of the titres.
*rSBA testing performed at PHE laboratories in UK
** tested at GSK laboratories

Immunogenicity in children aged 2-10 years

In MenACWY-TT-081, Nimenrix was demonstrated to be non-inferior to another licensed MenC-CRM vaccine in terms of vaccine response to group C [94.8% (95% CI: 91.4; 97.1) and 95.7% (95% CI: 89.2; 98.8) respectively], The GMT was lower for the Nimenrix group [2795 (95% CI: 2393; 3263)] versus the MenC-CRM vaccine [5292 (95% CI: 3815; 7340)].

In MenACWY-TT-038, 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) (See Table 8).

Table 8: Bactericidal antibody responses (rSBA*) to Nimenrix and the ACWY-PS vaccine in children aged 2-10 years 1 month after vaccination (study MenACWY-TT-038)

Meningococcal 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 the proportion of subjects with:

- rSBA titres ≥32 for initially seronegative subjects (i.e., pre-vaccination rSBA titre <8)
- at least a 4-fold increase in rSBA titres from pre- to post-vaccination for initially seropositive subjects (i.e., pre-vaccination rSBA titre ≥8)

* tested at GSK laboratories

Persistence of the immune response was evaluated in children initially vaccinated in MenACWY-TT-081 (Table 9).

Table 9: 44 months persistence data in children 2-10 years of age at vaccination (Study MenACWY-TT-088; extension of study 081)

Meningococcal Group	Vaccine Group	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)
		44	189	85.7% (79.9; 90.4)	307 (224; 423)	89	25.8% (17.1; 36.2)	4.8 (3.4; 6.7)
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)
		44	189	37.0% (30.1; 44.3)	14.5 (10.9; 19.2)	82	76.8% (66.2; 85.4)	36.4 (23.1; 57.2)
	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)
		44	66	45.5% (33.1; 58.2)	31.0 (16.6; 58.0)	31	64.5% (45.4; 80.8)	38.8 (13.3; 113)
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)
		44	189	68.3% (61.1; 74.8)	103 (72.5; 148)	87	80.5% (70.6; 88.2)	64.3 (42.7; 96.8)
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)
		44	189	62.4% (55.1; 69.4)	78.9 (54.6; 114)	76	82.9% (72.5; 90.6)	127 (78.0; 206)

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

Persistence of the immune response was evaluated by hSBA 1 year after vaccination in children 6-10 years of age who were initially vaccinated in study MenACWY-TT-027 (Table 10) (see section 4.4).

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

Meningococcal Group	Vaccine group	1 month post-vaccination (study MenACWY-TT-027)			1 year persistence (study MenACWY-TT-028)		
		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)	156 (99.3;244)	105	95.2% (89.2;98.4)	129 (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 (99.9;178)	103	100% (96.5;100)	257 (218;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)	106	99.1% (94.9;100)	265 (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

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

In two clinical studies, conducted in adolescents 11-17 years of age (study MenACWY-TT-036) and in adults 18-55 years of age (study MenACWY-TT-035), either one dose of Nimenrix or one dose of the ACWY-PS vaccine were administered.

Nimenrix was demonstrated to be immunologically non-inferior to the ACWY-PS vaccine in terms of vaccine response as defined above (Table 11).

Table 11: Bactericidal antibody responses (rSBA*) to Nimenrix and the ACWY-PS vaccine in adolescents aged 11-17 years and adults aged ≥ 18 years 1 month after vaccination

Study (Age range)	Meningococcal Group	Nimenrix			ACWY-PS vaccine		
		N	VR (95%CI)	GMT (95%CI)	N	VR (95%CI)	GMT (95%CI)
Study 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)
Study 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
* tested at GSK laboratories

Persistence of the immune response was evaluated up to 5 years after vaccination in adolescents primed in study MenACWY-TT-036 (Table 12).

Table 12: 5 years persistence data (rSBA*) in adolescents aged 11-17 years at vaccination

Meningococcal 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 the immune response was evaluated by hSBA up to 5 years after vaccination in adolescents and adults initially vaccinated in MenACWY-TT-052 (Table 13) (see section 4.4).

Table 13: 1 month post-vaccination (Study MenACWY-TT-052) and 5 years (Study MenACWY-TT-059) persistence data (hSBA*) in adolescents and adults 11-25 years of age

Meningococcal Group	Vaccine Group	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)
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)
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)
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)

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

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).

Booster response for subjects previously vaccinated with a conjugate meningococcal vaccine against *Neisseria meningitidis*

Nimenrix booster vaccination in subjects previously primed with a monovalent (MenC-CRM) or a quadrivalent conjugate meningococcal vaccine (MenACWY-TT) was studied in subjects from 12 months of age onwards who received a booster vaccination. Robust anamnestic responses to the antigen(s) in the priming vaccine were observed.

Response to Nimenrix in subjects previously vaccinated with a plain polysaccharide vaccine against *Neisseria meningitidis*

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 a 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. An immune response (rSBA titre ≥8) was observed against all groups (A, C, W-135, Y) in all subjects regardless of the meningococcal vaccine history. The rSBA GMTs were significantly lower in the subjects who had received a dose of ACWY-PS vaccine 30-42 months prior to Nimenrix, however 100% of subjects achieved rSBA titers ≥8 for all four meningococcal groups (A, C, W-135, Y) (see section 4.4).

The European Medicines Agency has deferred the obligation to submit the results of studies with Nimenrix in one or more subsets of the paediatric population in the prevention of meningococcal disease caused by *Neisseria meningitidis* group A, C, W-135 and Y (see section 4.2 for information on paediatric use).

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Sucrose
Trometamol

Solvent:

Sodium chloride
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

3 years

After reconstitution:

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.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder in a vial (type I glass) with a stopper (butyl rubber) and solvent in a pre-filled syringe with a stopper (butyl rubber).
Pack sizes of 1 and 10 with or without needles.

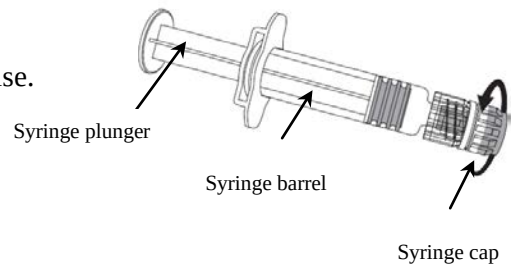
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

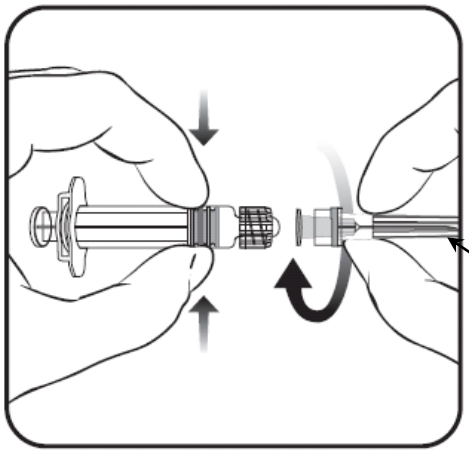
Nimenrix must be reconstituted by adding the entire content of the pre-filled syringe of solvent to the vial containing the powder.
To attach the needle to the syringe, refer to the below picture. However, the syringe provided with Nimenrix might be slightly different (without screw thread) than the syringe described in the picture. In that case, the needle should be attached without screwing.

1. Holding the syringe **barrel** in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.



2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock (See picture).

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.

A new needle should be used to administer the vaccine.

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

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/767/001
EU/1/12/767/002
EU/1/12/767/003
EU/1/12/767/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 April 2012
Date of latest renewal: 16 February 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Nimenrix powder and solvent for solution for injection in ampoule
Meningococcal group A, C, W-135 and Y conjugate vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (0.5 ml) contains:

Neisseria meningitidis group A polysaccharide[1]	5 micrograms
Neisseria meningitidis group C polysaccharide[1]	5 micrograms
Neisseria meningitidis group W-135 polysaccharide[1]	5 micrograms
Neisseria meningitidis group Y polysaccharide[1]	5 micrograms
[1]conjugated to tetanus toxoid carrier protein	44 micrograms

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
The powder or cake is white.
The solvent is clear and colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Nimenrix should be used in accordance with available official recommendations.

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).

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).

Previously vaccinated children from 12 months of age, adolescents and adults
Nimenrix may be given as a booster dose in individuals who have previously received primary vaccination with a conjugated or plain polysaccharide meningococcal vaccine (see sections 4.4 and 5.1).

Method of administration

Immunisation should be carried out by intramuscular injection only.

In infants, the recommended injection site is the anterolateral aspect of the thigh. In individuals from 1 year of age, the recommended injection site is the anterolateral aspect of the thigh or the deltoid muscle (see sections 4.4 and 4.5).

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

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.

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

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 especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

Thrombocytopenia and coagulation disorders

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.

Safety and immunogenicity have not been assessed in patients with increased susceptibility to meningococcal infection due to conditions such as terminal complement deficiencies and anatomic or functional asplenia. In these individuals, an adequate immune response may not be elicited.

Protection against meningococcal disease
Nimenrix will only confer protection against *Neisseria meningitidis* group A, C, W-135 and Y. The vaccine will not protect against any other *Neisseria meningitidis* groups.

A protective immune response may not be elicited in all vaccinees.
Effect of prior vaccination with plain polysaccharide meningococcal vaccine
Subjects previously vaccinated with a plain polysaccharide meningococcal vaccine and vaccinated with Nimenrix 30 to 42 months later had lower Geometric Mean Titres (GMTs) measured with rabbit complement serum bactericidal assay (rSBA) than subjects who had not been vaccinated with any meningococcal vaccine in the preceding 10 years (see section 5.1). The clinical relevance of this observation is unknown.

Effect of pre-vaccination antibody to tetanus toxoid
The safety and immunogenicity of Nimenrix was evaluated when it was sequentially administered or co-administered with a vaccine containing, diphtheria and tetanus toxoids, acellular pertussis, inactivated polioviruses (1, 2 and 3), hepatitis B surface antigen and *Haemophilus influenzae* type b polyribosyl ribose phosphate conjugated to tetanus toxoid (DTaP-HBV-IPV/Hib) in the second year of life. The administration of Nimenrix one month after the DTaP-HBV-IPV/Hib vaccine resulted in lower rSBA GMTs against groups A, C and W-135 compared with co-administration (see section 4.5). The clinical relevance of this observation is unknown.

Immune responses in toddlers aged 12-14 months
Toddlers aged 12-14 months had similar rSBA responses to groups A, C, W-135 and Y at one month after one dose of Nimenrix or at one month after two doses of Nimenrix given two months apart. A single dose was associated with lower human complement serum bactericidal assay (hSBA) titres to groups W-135 and Y compared with two doses given two months apart. Similar responses to groups A and C were observed after one or two doses (see section 5.1). The clinical relevance of the findings is unknown. If a toddler is expected to be at particular risk of invasive meningococcal disease due to exposure to groups W-135 and Y, consideration may be given to administering a second dose of Nimenrix after an interval of 2 months. Regarding waning of antibody against group A or group C 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

Following administration of Nimenrix there is a waning of serum bactericidal antibody titres against group A when using human complement in the assay (hSBA) (see section 5.1). The clinical relevance of the waning of hSBA antibody titres against group A is unknown. However, if an individual is expected to be at particular risk of exposure to group A and received a dose of Nimenrix more than approximately one year previously, consideration may be given to administering a booster dose.

A decline in antibody titres over time has been observed for groups A, C, W-135 and Y. 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 or Y (see section 5.1).

Effect of Nimenrix on anti-tetanus antibody concentrations

Although an increase of the anti-tetanus toxoid (TT) antibody concentrations was observed following vaccination with Nimenrix, Nimenrix does not substitute for tetanus immunisation.
Giving Nimenrix with or one month before a TT-containing vaccine in the second year of life does not impair the response to TT or significantly affect safety. No data are available beyond the age of 2 years.

4.5 Interaction with other medicinal products and other forms of interaction

In infants, Nimenrix can be given concomitantly with combined DTaP-HBV-IPV/Hib vaccines and with 10-valent pneumococcal conjugate vaccine.

From age 1 year 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.

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

Whenever possible, Nimenrix and a TT containing vaccine, such as DTaP-HBV-IPV/Hib vaccine, should 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). The clinical relevance of this observation is unknown. There was no impact of co-administration on immune responses to the other nine pneumococcal serotypes.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

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

Breast-feeding

It is unknown whether Nimenrix is excreted in human milk.

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

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

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.

However, some of the effects mentioned under section 4.8 “Undesirable effects” may affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of Nimenrix has been evaluated in clinical studies as follows:

- A single dose was administered to 9,621 subjects. 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.
- In a study in infants aged 6 to 12 weeks at the time of the first dose, 1052 subjects received at least one dose of a primary series of 2 or 3 doses of Nimenrix and 1008 received a booster dose at approximately 12 months of age.

In the 6-12 weeks and in the 12-14 months age groups who received 2 doses of Nimenrix given 2 months apart, the first and second doses were associated with similar local and systemic reactogenicity.

The local and general adverse reaction profile of a booster dose of Nimenrix after primary vaccination with Nimenrix or other conjugated or plain polysaccharide meningococcal vaccines, was similar to the local and general adverse reaction profile observed after primary vaccination with Nimenrix, except for gastrointestinal symptoms (including diarrhoea, vomiting, and nausea), which were very common.

Tabulated list of adverse reactions

Adverse reactions reported are listed according to the following frequency categories:

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)

Table 1 shows the adverse reactions reported from the studies in subjects aged from 6 weeks up to 55 years of age and post-marketing experience. Adverse reactions reported in subjects aged >55 years were similar to those observed in younger adults.

Table 1 Tabulated summary of adverse reactions by system organ class

System Organ Class	Frequency	Adverse reactions
Metabolism and nutrition disorders	Very common	Appetite lost
Psychiatric disorders	Very common	Irritability
	Uncommon	Insomnia Crying
Nervous system disorders	Very common	Drowsiness Headache
	Uncommon	Hypoaesthesia Dizziness
Gastrointestinal disorders	Common	Diarrhoea Vomiting Nausea*
Skin and subcutaneous tissue	Uncommon	Pruritus

Table 1 Tabulated summary of adverse reactions by system organ class		
System Organ Class	**Frequency**	**Adverse reactions**
disorders		Rash**
Musculoskeletal and connective tissue disorders	Uncommon	Myalgia Pain in extremity
General disorders and administration site conditions	Very common	Fever Swelling at injection site Pain at injection site Redness at injection site Fatigue
	Common	Injection site haematoma*
	Uncommon	Malaise Injection site induration Injection site pruritus Injection site warmth Injection site anaesthesia
	Unknown***	Extensive limb swelling at the injection site, frequently associated with erythema, sometimes involving the adjacent joint or swelling of the entire injected limb

*Nausea and Injection site haematoma occurred at a frequency of Uncommon in infants
**Rash occurred at a frequency of Common in infants
***ADR identified post-marketing

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, meningococcal vaccines, ATC code: J07AH08

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 *Neisseria meningitidis* group A, C, W-135 and Y when measured by assays using either rabbit complement (rSBA) or human complement (hSBA).

Immunogenicity in infants

In the clinical study in infants (MenACWY-TT-083), the first dose was administered at 6 to 12 weeks of age, the second dose was given after an interval of 2 months and a third (booster) dose was given at the age of approximately 12 months. DTaP-HBV-IPV/Hib and a 10-valent pneumococcal vaccine were co-administered. Nimenrix elicited a bactericidal antibody response against the four meningococcal groups. The response against group C was non-inferior to the one elicited by licensed MenC-CRM and MenC-TT vaccines in terms of percentages with rSBA titres ≥8 at one month after the second dose. See Table 2.

Table 2: Bactericidal antibody responses (rSBA*) and (hSBA) in infants after two doses given 2 months apart and after a booster dose at 12 months of age (Study MenACWY-TT-083)**

Meningococcal Group	Vaccine group		rSBA*			hSBA**		
			N	≥8 (95% CI)	GMT (95% CI)	N	≥8 (95% CI)	GMT (95% CI)
A	Nimenrix	Post dose 2[(1)]	456	97.4% (95.4; 98.6)	203 (182; 227)	202	96.5% (93.0; 98.6)	157 (131; 188)
		Post booster[(1)]	462	99.6% (98.4; 99.9)	1561 (1412; 1725)	214	99.5% (97.4;100)	1007 (836;1214)
C	Nimenrix	Post dose 2[(1)]	456	98.7% (97.2; 99.5)	612 (540; 693)	218	98.6% (96.0; 99.7)	1308 (1052; 1627)
		Post booster[(1)]	463	99.8% (98.8; 100)	1177 (1059; 1308)	221	99.5% (97.5; 100)	4992 (4086; 6100)
	MenC-CRM vaccine	Post dose 2[(1)]	455	99.6% (98.4; 99.9)	958 (850; 1079)	202	100% (98.2; 100)	3188 (2646; 3841)
		Post booster[(1)]	446	98.4% (96.8; 99.4)	1051 (920; 1202)	216	100% (98.3; 100)	5438 (4412; 6702)
	MenC-TT vaccine	Post dose 2[(1)]	457	100% (99.2; 100)	1188 (1080; 1307)	226	100% (98.4; 100)	2626 (2219; 3109)
		Post booster[(1)]	459	100% (99.2; 100)	1960 (1776; 2163)	219	100% (98.3; 100)	5542 (4765; 6446)
W	Nimenrix	Post dose 2[(1)]	455	99.1% (97.8; 99.8)	1605 (1383; 1862)	217	100% (98.3; 100)	753 (644; 882)
		Post booster[(1)]	462	99.8% (98.8; 100)	2777 (2485; 3104)	218	100% (98.3; 100)	5123 (4504; 5826)
Y	Nimenrix	Post dose 2[(1)]	456	98.2% (96.6; 99.2)	483 (419; 558)	214	97.7% (94.6; 99.2)	328 (276; 390)
		Post booster[(1)]	462	99.4% (99.1; 99.9)	881 (787; 986)	217	100% (98.3; 100)	2954 (2498; 3493)

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

(1) blood sampling performed 21 to 48 days post vaccination

Immunogenicity in toddlers aged 12-23 months

In clinical studies MenACWY-TT-039 and MenACWY-TT-040 a single dose of Nimenrix elicited rSBA responses against the four meningococcal groups, with a response against group C that was comparable to the one elicited by the licensed MenC-CRM vaccine in terms of percentages with rSBA titres ≥8 (Table 3).

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

Meningococcal Group	Vaccine group	Study MenACWY-TT-039(1)			Study MenACWY-TT-040(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 vaccine	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 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

In study MenACWY-TT-039, serum bactericidal activity was also measured using human serum as the source of complement (hSBA) as a secondary endpoint (Table 4).

Table 4: Bactericidal antibody responses (hSBA*) in toddlers aged 12-23 months

Meningococcal Group	Vaccine group	N	Study MenACWY-TT-039(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 vaccine	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

In Study Men ACWY-TT-104 the immune response following one or two doses of Nimenrix given 2 months apart was evaluated one month 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 5).

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

Meningococcal Group	Vaccine group	Timing	Study MenACWY-TT-104[(1)]		
			N	≥8 (95%CI)	GMT (95% CI)
A	Nimenrix 1 dose	Post dose 1	180	97.8% (94.4, 99.4)	1437 (1118, 1847)
	Nimenrix 2 doses	Post dose 1	158	96.8% (92.8, 99.0)	1275 (970, 1675)
		Post dose 2	150	98.0% (94.3, 99.6)	1176 (922, 1501)
C	Nimenrix 1 dose	Post dose 1	179	95.0% (90.7, 97.7)	452 (346, 592)
	Nimenrix 2 doses	Post dose 1	157	95.5% (91.0, 98.2)	369 (281, 485)
		Post dose 2	150	98.7% (95.3, 99.8)	639 (522, 783)
W-135	Nimenrix 1 dose	Post dose 1	180	95.0% (90.8, 97.7)	2120 (1601, 2808)
	Nimenrix 2 doses	Post dose 1	158	94.9% (90.3, 97.8)	2030 (1511, 2728)
		Post dose 2	150	100% (97.6, 100)	3533 (2914, 4283)
Y	Nimenrix 1 dose	Post dose 1	180	92.8% (88.0, 96.1)	952 (705, 1285)
	Nimenrix 2 doses	Post dose 1	157	93.6% (88.6, 96.9)	933 (692, 1258)
		Post dose 2	150	99.3% (96.3, 100)	1134 (944, 1360)

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

[(1)] blood sampling performed 21-48 days post vaccination

*tested at Public Health England laboratories

In study MenACWY-TT-104, serum bactericidal activity was also measured using hSBA as a secondary endpoint. Nimenrix elicited bactericidal responses against groups W-135 and Y that were higher in terms of % with hSBA titre ≥8 when two doses were given compared with one. Similar responses in terms of % with hSBA titre ≥8 were observed with groups A and C (Table 6).

Table 6: Bactericidal antibody responses (hSBA)* in toddlers aged 12-14 months

Meningococcal Group	Vaccine group	Timing	Study MenACWY-TT-104[(1)]		
			N	≥8 (95%CI)	GMT (95% CI)
A	Nimenrix 1 dose	Post dose 1	74	95.9% (88.6, 99.2)	118 (87, 160)
	Nimenrix 2 doses	Post dose 1	66	97.0% (89.5, 99.6)	133 (98, 180)
		Post dose 2	66	97.0% (89.5, 99.6)	170 (126, 230)
C	Nimenrix 1 dose	Post dose 1	78	98.7% (93.1, 100)	152 (105, 220)
	Nimenrix 2 doses	Post dose 1	70	95.7% (88.0, 99.1)	161 (110, 236)
		Post dose 2	69	100% (94.8, 100)	1753 (1278, 2404)
W-135	Nimenrix 1 dose	Post dose 1	72	62.5% (50.3, 73.6)	27 (16, 47)
	Nimenrix 2 doses	Post dose 1	61	68.9% (55.7, 80.1)	26 (16, 43)
		Post dose 2	70	97.1% (90.1, 99.7)	757 (550, 1041)
Y	Nimenrix 1 dose	Post dose 1	71	67.6% (55.5, 78.20)	41 (24, 71)
	Nimenrix 2 doses	Post dose 1	56	64.3% (50.4, 76.6)	32 (18, 58)
		Post dose 2	64	95.3% (86.9, 99.0)	513 (339, 775)

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

[(1)] blood sampling performed 21-48 days post vaccination

*tested at GSK laboratories

Persistence of the immune response was evaluated by rSBA and hSBA up to 5 years in children initially vaccinated in study MenACWY-TT-027 (Table 7).

Table 7: 5 years persistence data in toddlers aged 12-23 months at vaccination (study MenACWY-TT-032; extension of study 027)

Meningococcal Group	Vaccine Group	Time-point (year)	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. A selection bias mainly due to revaccination of subjects with group C rSBA titres <8 and their exclusion from subsequent time-point(s) may have led to an overestimation of the titres.
*rSBA testing performed at PHE laboratories in UK
** tested at GSK laboratories

Immunogenicity in children aged 2-10 years

In MenACWY-TT-081, Nimenrix was demonstrated to be non-inferior to another licensed MenC-CRM vaccine in terms of vaccine response to group C [94.8% (95% CI: 91.4; 97.1) and 95.7% (95% CI: 89.2; 98.8) respectively], The GMT was lower for the Nimenrix group [2795 (95% CI: 2393; 3263)] versus the MenC-CRM vaccine [5292 (95% CI: 3815; 7340)].

In MenACWY-TT-038, 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) (See Table 8).

Table 8: Bactericidal antibody responses (rSBA*) to Nimenrix and the ACWY-PS vaccine in children aged 2-10 years 1 month after vaccination (study MenACWY-TT-038)

Meningococcal 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 the proportion of subjects with:

- rSBA titres ≥ 32 for initially seronegative subjects (i.e., pre-vaccination rSBA titre < 8)
- at least a 4-fold increase in rSBA titres from pre- to post-vaccination for initially seropositive subjects (i.e., pre-vaccination rSBA titre ≥ 8)

* tested at GSK laboratories

Persistence of the immune response was evaluated in children initially vaccinated in MenACWY-TT-081 (Table 9).

Table 9: 44 months persistence data in children 2-10 years of age at vaccination (Study MenACWY-TT-088; extension of study 081)

Meningococcal Group	Vaccine Group	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)
		44	189	85.7% (79.9; 90.4)	307 (224; 423)	89	25.8% (17.1; 36.2)	4.8 (3.4; 6.7)
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)
		44	189	37.0% (30.1; 44.3)	14.5 (10.9; 19.2)	82	76.8% (66.2; 85.4)	36.4 (23.1; 57.2)
	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)
		44	66	45.5% (33.1; 58.2)	31.0 (16.6; 58.0)	31	64.5% (45.4; 80.8)	38.8 (13.3; 113)
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)
		44	189	68.3% (61.1; 74.8)	103 (72.5; 148)	87	80.5% (70.6; 88.2)	64.3 (42.7; 96.8)
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)
		44	189	62.4% (55.1; 69.4)	78.9 (54.6; 114)	76	82.9% (72.5; 90.6)	127 (78.0; 206)

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

Persistence of the immune response was evaluated by hSBA 1 year after vaccination in children 6-10 years of age who were initially vaccinated in study MenACWY-TT-027 (Table 10) (see section 4.4).

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

Meningococcal Group	Vaccine group	1 month post-vaccination (study MenACWY-TT-027)			1 year persistence (study MenACWY-TT-028)		
		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)	156 (99.3;244)	105	95.2% (89.2;98.4)	129 (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 (99.9;178)	103	100% (96.5;100)	257 (218;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)	106	99.1% (94.9;100)	265 (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

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

In two clinical studies, conducted in adolescents 11-17 years of age (study MenACWY-TT-036) and in adults 18-55 years of age (study MenACWY-TT-035), either one dose of Nimenrix or one dose of the ACWY-PS vaccine were administered.

Nimenrix was demonstrated to be immunologically non-inferior to the ACWY-PS vaccine in terms of vaccine response as defined above (Table 11).

Table 11: Bactericidal antibody responses (rSBA*) to Nimenrix and the ACWY-PS vaccine in adolescents aged 11-17 years and adults aged ≥ 18 years 1 month after vaccination

Study (Age range)	Meningococcal Group	Nimenrix			ACWY-PS vaccine		
		N	VR (95%CI)	GMT (95%CI)	N	VR (95%CI)	GMT (95%CI)
Study 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;	219	78.5% (72.5; 83.8)	5066 (4463; 5751)

Study (Age range)	Meningococcal Group	Nimenrix			ACWY-PS vaccine		
		N	VR (95%CI)	GMT (95%CI)	N	VR (95%CI)	GMT (95%CI)
				15069)			
Study 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
* tested at GSK laboratories

Persistence of the immune response was evaluated up to 5 years after vaccination in adolescents primed in study MenACWY-TT-036 (Table 12).

Table 12: 5 years persistence data (rSBA*) in adolescents aged 11-17 years at vaccination

Meningococcal 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 the immune response was evaluated by hSBA up to 5 years after vaccination in adolescents and adults initially vaccinated in MenACWY-TT-052 (Table 13) (see section 4.4).

Table 13: 1 month post-vaccination (Study MenACWY-TT-052) and 5 years (Study MenACWY-TT-059) persistence data (hSBA*) in adolescents and adults 11-25 years of age

Meningococcal Group	Vaccine Group	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)
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)
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)
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)

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

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).

Booster response for subjects previously vaccinated with a conjugate meningococcal vaccine against *Neisseria meningitidis*

Nimenrix booster vaccination in subjects previously primed with a monovalent (MenC-CRM) or a quadrivalent conjugate meningococcal vaccine (MenACWY-TT) was studied in subjects from 12 months of age onwards who received a booster vaccination. Robust anamnestic responses to the antigen(s) in the priming vaccine were observed.

Response to Nimenrix in subjects previously vaccinated with a plain polysaccharide vaccine against *Neisseria meningitidis*

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 a 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. An immune response (rSBA titre ≥8) was observed against all groups (A, C, W-135, Y) in all subjects regardless of the meningococcal vaccine history. The rSBA GMTs were significantly lower in the subjects who had received a dose of ACWY-PS vaccine 30-42 months prior to Nimenrix, however 100% of subjects achieved rSBA titers ≥8 for all four meningococcal groups (A, C, W-135, Y) (see section 4.4).

The European Medicines Agency has deferred the obligation to submit the results of studies with Nimenrix in one or more subsets of the paediatric population in the prevention of meningococcal disease caused by *Neisseria meningitidis* group A, C, W-135 and Y (see section 4.2 for information on paediatric use).

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Sucrose
Trometamol

Solvent:

Sodium chloride
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

3 years

After reconstitution:

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.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder in a vial (type I glass) with a stopper (butyl rubber) and solvent in an ampoule (type I glass).
Pack sizes of 1, 10 and 100

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for reconstitution of the vaccine with the solvent presented in ampoules

Nimenrix must be reconstituted by adding the entire content of the ampoule of solvent to the vial containing the powder.

1. Break the top of the ampoule, draw up the solvent with a syringe and add the solvent to the powder.
2. 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.

A new needle should be used to administer the vaccine.

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

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/767/005
EU/1/12/767/006
EU/1/12/767/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 April 2012
Date of latest renewal: 16 February 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance
GlaxoSmithKline Biologicals S.A.
89, rue de l'Institut
B-1330 Rixensart
Belgium

GlaxoSmithKine Biologicals Kft.
Homoki Nagy István utca 1.
2100 Gödöllö
Hungary

GlaxoSmithKline Biologicals S.A.
Parc de la Noire Epine
20, rue Fleming
B-1300 Wavre
Belgium

Name and address of the manufacturer(s) responsible for batch release

Pfizer Manufacturing Belgium N.V.
Rijksweg 12
B-2870 Puurs
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change in the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Study to evaluate immediate and longer term antibody titres elicited by one or two doses of Nimenrix administered in children aged 12-23 months. The safety and antibody persistence data up to year 5 and the data on co-administration of MenACWY-TT with Prevenar 13 will be provided in sequential study reports at 1, 3 and 5 years after vaccination.	1 year CSR Q1 2017 3 year CSR Q1 2019 5 year CSR Q1 2021

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
1 VIAL AND 1 PRE-FILLED SYRINGE WITHOUT NEEDLE
1 VIAL AND 1 PRE-FILLED SYRINGE WITH 2 NEEDLES
10 VIALS AND 10 PRE-FILLED SYRINGES WITHOUT NEEDLE
10 VIALS AND 10 PRE-FILLED SYRINGES WITH 20 NEEDLES

1. NAME OF THE MEDICINAL PRODUCT

Nimenrix powder and solvent for solution for injection in pre-filled syringe
Meningococcal group A, C, W-135 and Y conjugate vaccine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1 dose (0.5 ml) contains 5 micrograms of *Neisseria meningitidis* group A, C, W-135 and Y polysaccharides.

3. LIST OF EXCIPIENTS

Excipients:
Sucrose
Trometamol
Sodium chloride
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection in a pre-filled syringe

1 vial: powder
1 pre-filled syringe: solvent
1 dose (0.5 ml)

10 vials: powder
10 pre-filled syringes: solvent
10 x 1 dose (0.5 ml)

1 vial: powder
1 pre-filled syringe: solvent
2 needles
1 dose (0.5 ml)

10 vials: powder
10 pre-filled syringes: solvent
20 needles
10 x 1 dose (0.5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use.

Shake well before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.
After reconstitution, use promptly.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/767/001 – pack of 1 without needle
EU/1/12/767/002 – pack of 10 without needle
EU/1/12/767/003 – pack of 1 with 2 needles
EU/1/12/767/004 – pack of 10 with 20 needles

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
1 VIAL AND 1 AMPOULE
10 VIALS AND 10 AMPOULES
100 VIAL AND 100 AMPOULES

1. NAME OF THE MEDICINAL PRODUCT

Nimenrix powder and solvent for solution for injection in ampoule
Meningococcal group A, C, W-135 and Y conjugate vaccine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1 dose (0.5 ml) contains 5 micrograms of *Neisseria meningitidis* group A, C, W-135 and Y polysaccharides.

3. LIST OF EXCIPIENTS

Excipients:
Sucrose
Trometamol
Sodium chloride
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection in ampoule

1 vial: powder
1 ampoule: solvent
1 dose (0.5 ml)

10 vials: powder
10 ampoules: solvent
10 x 1 dose (0.5 ml)

100 vials: powder
100 ampoules: solvent
100 x 1 dose (0.5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use.
Shake well before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.
After reconstitution, use promptly.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/767/005 – pack of 1
EU/1/12/767/006 – pack of 10
EU/1/12/767/007 – pack of 100

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED SYRINGE WITH SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Nimenrix
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 ml)

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
AMPOULE WITH SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Nimenrix
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 ml)

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL WITH MEN ACWY CONJUGATE POWDER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Powder for Nimenrix
MenACWY Conjugate
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Nimenrix powder and solvent for solution for injection in pre-filled syringe
Meningococcal group A, C, W-135 and Y conjugate vaccine

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This vaccine has been prescribed for you or your child. Do not pass it on to others.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

This leaflet has been written assuming the person receiving the vaccine is reading it, but it can be given to adults and children so you may be reading it for your child.

What is in this leaflet

1. What Nimenrix is and what it is used for

What Nimenrix is and what it is used for
Nimenrix is a vaccine which helps protect against infections caused by bacteria (germs) called "*Neisseria meningitidis"* types A, C, W-135 and Y.
"Neisseria meningitidis" types A, C, W-135 and Y bacteria can cause serious illnesses such as:
- meningitis - an infection of the tissue that lines the brain and spinal cord.
- septicaemia - an infection of the blood.

These infections are passed easily from person to person and can cause death if not treated.
Nimenrix may be given to adults, adolescents, children and infants over the age of 6 weeks.

How Nimenrix works
Nimenrix helps your body to produce its own protection (antibodies) against the bacteria. These antibodies help protect you against the diseases.

Nimenrix will only protect against infections caused by the bacteria "*Neisseria meningitidis"* types A, C, W-135 and Y.

2. What you need to know before you receive Nimenrix

Nimenrix should not be given if:
- you are allergic to the active substances or any of the other ingredients in this vaccine (listed in section 6).
  Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue. **See your doctor immediately if you notice any of these**.

If you are not sure, talk to your doctor or nurse before you receive Nimenrix.

Warnings and precautions:
Check with your doctor or nurse before you receive this vaccine if:

- you have an infection with a high temperature (over 38°C). If this applies to you, the vaccination will not be given until you are feeling better. A minor infection such as a cold should not be a problem. However, talk to your doctor or nurse first.
- you have a bleeding problem or you bruise easily.

If any of the above apply to you (or you are not sure), talk to your doctor or nurse before you receive Nimenrix.

Nimenrix may not fully protect everyone who is vaccinated. If you have a weak immune system (such as due to HIV infection or medicines that affect the immune system) you may not get a full benefit from Nimenrix.

Fainting can occur (mostly in adolescents) following, or even before, any needle injection. Therefore tell the doctor or nurse if you or your child fainted with a previous injection.

Other medicines and Nimenrix
Tell your doctor or nurse if you are taking or have recently taken any other medicines, including other vaccines and medicines obtained without a prescription.

Nimenrix may not work as well if you are taking medicines that affect your immune system.

From age 1 year 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.

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

Whenever possible, Nimenrix and a TT containing vaccine, such as DTaP-HBV-IPV/Hib vaccine, should be co-administered or Nimenrix should be administered at least one month before the TT containing vaccine.

A different injection site will be used for each vaccine.

Pregnancy and breast-feeding
If you are pregnant, think you may be pregnant, plan to become pregnant or are breast-feeding, you must tell your doctor before receiving Nimenrix.

Driving and using machines
Nimenrix is not likely to affect your ability to drive or use machines. However, do not drive or use any machines if you are feeling unwell.

3. How Nimenrix is given

Nimenrix will be given to you by a doctor or nurse.
Nimenrix is always injected into a muscle, usually in the upper arm or thigh.

<u>Infants from the age of 6 weeks to 12 weeks of age</u>
2 injections given two months apart at e.g. 2 and 4 months of age (the first injection may be given from the age of 6 weeks).
At 12 months of age, an additional injection (booster) will be given.

You will be informed when your child should come back for their next injection. If your child misses a scheduled injection, it is important that you make another appointment.

Make sure your child finishes the complete vaccination course.

Children above 1 year of age, adolescents and adults:
One dose of vaccine should be administered.

Please tell your doctor if you have received a previous injection with another meningococcal vaccine than Nimenrix.

Your doctor will tell you if and when you need an additional dose of Nimenrix, especially if you or your child:
- received your first dose aged 12-23 months and could be at risk of infection caused by *Neisseria meningitidis* types A, C, W-135 and Y
- were aged more than 2 years when first vaccinated and could be at risk of infection caused by *Neisseria meningitidis* type A

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

Very common (these may occur with more than 1 in 10 doses of the vaccine):
- fever
- tiredness (fatigue)
- headache
- feeling drowsy
- loss of appetite
- feeling irritable
- swelling, pain and redness where the injection is given.

Common (these may occur with up to 1 in 10 doses of the vaccine):
- bruising (haematoma) where the injection is given
- stomach and digestion problems such as diarrhoea, vomiting and nausea
- rash (infants).

Uncommon (these may occur with up to 1 in 100 doses of the vaccine):
- rash
- crying
- itching
- feeling dizzy
- aching muscles
- pain in the arms or legs
- generally feeling unwell
- difficulty sleeping
- decreased feeling or sensitivity, especially in the skin
- reactions where the injection is given such as itching, a feeling of warmth or numbness or a hard lump.

Not known: frequency cannot be estimated from the available data
- injection site swelling and redness; this may affect a large area of the vaccinated limb

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting

system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Nimenrix

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C).
- Store in the original package in order to protect from light.
- Do not freeze.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Nimenrix contains

- The active substances are:
  - After reconstitution, 1 dose (0.5 ml) contains:

Neisseria meningitidis group A polysaccharide[1]	5 micrograms
Neisseria meningitidis group C polysaccharide[1]	5 micrograms
Neisseria meningitidis group W-135 polysaccharide[1]	5 micrograms
Neisseria meningitidis group Y polysaccharide[1]	5 micrograms
[1]conjugated to tetanus toxoid carrier protein	44 micrograms

- The other ingredients are:
  - In the powder: sucrose and trometamol
  - In the solvent: sodium chloride and water for injections

What Nimenrix looks like and contents of the pack

Nimenrix is a powder and a solvent for solution for injection.
Nimenrix is supplied as a white powder or cake in a single dose glass vial and a clear and colourless solvent in a pre-filled syringe.
These must be mixed together before use. The mixed vaccine will appear as a clear colourless solution.
Nimenrix is available in packs of 1 or 10 with or without needles.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

Manufacturer responsible for batch release:
Pfizer Manufacturing Belgium N.V.
Rijksweg 12
B-2870 Puurs
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Luxembourg/Luxemburg
Pfizer S.A./N.V.
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Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana
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Pfizer Limited
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This leaflet was last revised in {MM/YYYY}

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

The vaccine is for intramuscular use only. Do not administer intravascularly, intradermally or subcutaneously.

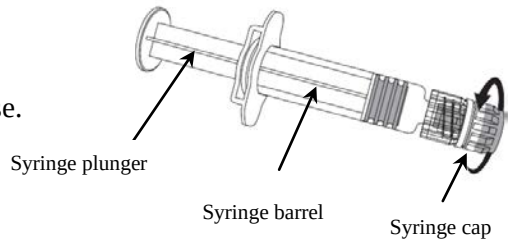
If Nimenrix is co-administered with other vaccines, different injection sites should be used.

Nimenrix should not be mixed with other vaccines.

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

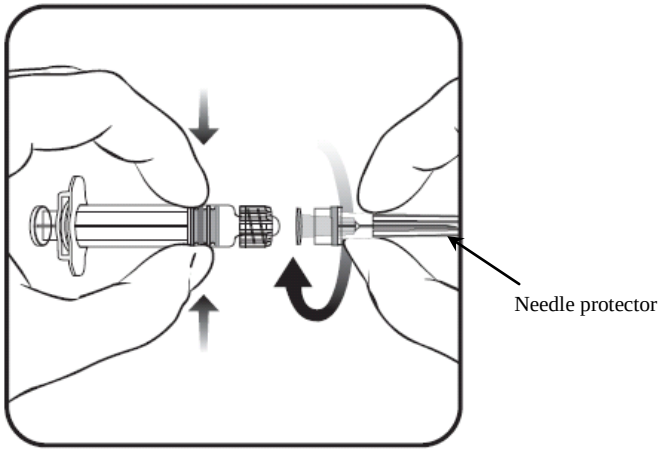
Nimenrix must be reconstituted by adding the entire content of the pre-filled syringe of solvent to the vial containing the powder.
To attach the needle to the syringe, refer to the picture. However, the syringe provided with Nimenrix might be slightly different (without screw thread) than the syringe described in the picture. In that case the needle should be attached without screwing.

1. Holding the syringe **barrel** in one hand
(avoid holding the syringe plunger),
unscrew the syringe cap by twisting it anticlockwise.



2. To attach the needle to the syringe,
twist the needle clockwise into the syringe
until you feel it lock (See picture).

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.

A new needle should be used to administer the vaccine.

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

Package leaflet: Information for the user

Nimenrix powder and solvent for solution for injection in ampoule
Meningococcal group A, C, W-135 and Y conjugate vaccine

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This vaccine has been prescribed for you or your child. Do not pass it on to others.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

This leaflet has been written assuming the person receiving the vaccine is reading it, but it can be given to adults and children so you may be reading it for your child.

What is in this leaflet

1. What Nimenrix is and what it is used for

What Nimenrix is and what it is used for
Nimenrix is a vaccine which helps protect against infections caused by bacteria (germs) called "*Neisseria meningitides"* types A, C, W-135 and Y.
"Neisseria meningitidis" types A, C, W-135 and Y bacteria can cause serious illnesses such as:
- meningitis - an infection of the tissue that lines the brain and spinal cord.
- septicaemia - an infection of the blood.

These infections are passed easily from person to person and can cause death if not treated.
Nimenrix may be given to adults, adolescents, children and infants over the age of 6 weeks.

How Nimenrix works
Nimenrix helps your body to produce its own protection (antibodies) against the bacteria. These antibodies help protect you against the diseases.
Nimenrix will only protect against infections caused by the bacteria "*Neisseria meningitidis"* types A, C, W-135 and Y.

2. What you need to know before you receive Nimenrix

Nimenrix should not be given if:
- you are allergic to the active substances or any of the other ingredients in this vaccine (listed in section 6).
  Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue. **See your doctor immediately if you notice any of these**.

If you are not sure, talk to your doctor or nurse before you receive Nimenrix.

Warnings and precautions:
Check with your doctor or nurse before you receive this vaccine if:

- you have an infection with a high temperature (over 38°C). If this applies to you, the vaccination will not be given until you are feeling better. A minor infection such as a cold should not be a problem. However, talk to your doctor or nurse first.
- you have a bleeding problem or you bruise easily.

If any of the above apply to you (or you are not sure), talk to your doctor or nurse before you receive Nimenrix.

Nimenrix may not fully protect everyone who is vaccinated. If you have a weak immune system (such as due to HIV infection or medicines that affect the immune system) you may not get a full benefit from Nimenrix.

Fainting can occur (mostly in adolescents) following, or even before, any needle injection. Therefore tell the doctor or nurse if you or your child fainted with a previous injection.

Other medicines and Nimenrix
Tell your doctor or nurse if you are taking or have recently taken any other medicines, including other vaccines and medicines obtained without a prescription.

Nimenrix may not work as well if you are taking medicines that affect your immune system.

From age 1 year 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.

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

Whenever possible, Nimenrix and a TT containing vaccine, such as DTaP-HBV-IPV/Hib vaccine, should be co-administered or Nimenrix should be administered at least one month before the TT containing vaccine.

A different injection site will be used for each vaccine.

Pregnancy and breast-feeding
If you are pregnant, think you may be pregnant, plan to become pregnant or are breast-feeding, you must tell your doctor before receiving Nimenrix.

Driving and using machines
Nimenrix is not likely to affect your ability to drive or use machines. However, do not drive or use any machines if you are feeling unwell.

3. How Nimenrix is given

Nimenrix will be given to you by a doctor or nurse.
Nimenrix is always injected into a muscle, usually in the upper arm or thigh.

<u>Infants from the age of 6 weeks to 12 weeks of age:</u>
2 injections given two months apart at e.g. 2 and 4 months of age (the first injection may be given from the age of 6 weeks).
At 12 months of age, an additional injection (booster) will be given.

You will be informed when your child should come back for their next injection. If your child misses a scheduled injection, it is important that you make another appointment.

Make sure your child finishes the complete vaccination course.

Children above 1 year of age, adolescents and adults:
One dose of vaccine should be administered.

Please tell your doctor if you have received a previous injection with another meningococcal vaccine than Nimenrix.

Your doctor will tell you if and when you need an additional dose of Nimenrix, especially if you or your child:

- received your first dose aged 12-23 months and could be at risk of infection caused by *Neisseria meningitidis* types A, C, W-135 and Y
- were aged more than 2 years when first vaccinated and could be at risk of infection caused by *Neisseria meningitidis* type A

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

Very common (these may occur with more than 1 in 10 doses of the vaccine):

- fever
- tiredness (fatigue)
- headache
- feeling drowsy
- loss of appetite
- feeling irritable
- swelling, pain and redness where the injection is given.

Common (these may occur with up to 1 in 10 doses of the vaccine):

- bruising (haematoma) where the injection is given
- stomach and digestion problems such as diarrhoea, vomiting and nausea.
- rash (infants).

Uncommon (these may occur with up to 1 in 100 doses of the vaccine):

- rash
- crying
- itching
- feeling dizzy
- aching muscles
- pain in the arms or legs
- generally feeling unwell
- difficulty sleeping
- decreased feeling or sensitivity, especially in the skin
- reactions where the injection is given such as itching, a feeling of warmth or numbness or a hard lump.

Not known: frequency cannot be estimated from the available data

- injection site swelling and redness; this may affect a large area of the vaccinated limb

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting

system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Nimenrix

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C).
- Store in the original package in order to protect from light.
- Do not freeze.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Nimenrix contains

- The active substances are:
  - After reconstitution, 1 dose (0.5 ml) contains:

Neisseria meningitidis group A polysaccharide[1]	5 micrograms
Neisseria meningitidis group C polysaccharide[1]	5 micrograms
Neisseria meningitidis group W-135 polysaccharide[1]	5 micrograms
Neisseria meningitidis group Y polysaccharide[1]	5 micrograms
[1]conjugated to tetanus toxoid carrier protein	44 micrograms

- The other ingredients are:
  - In the powder: sucrose and trometamol
  - In the solvent: sodium chloride and water for injections

What Nimenrix looks like and contents of the pack

Nimenrix is a powder and a solvent for solution for injection.
Nimenrix is supplied as a white powder or cake in a single dose glass vial and a clear and colourless solvent in an ampoule.
These must be mixed together before use. The mixed vaccine will appear as a clear colourless solution.
Nimenrix is available in packs of 1, 10 or 100.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
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Manufacturer responsible for batch release:
Pfizer Manufacturing Belgium N.V.
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Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

The following information is intended for healthcare professionals only:

The vaccine is for intramuscular use only. Do not administer intravascularly, intradermally or subcutaneously.

If Nimenrix is co-administered with other vaccines, different injection sites should be used.

Nimenrix should not be mixed with other vaccines.

Instructions for reconstitution of the vaccine with the solvent presented in ampoules:

Nimenrix must be reconstituted by adding the entire content of the ampoule of solvent to the vial containing the powder.
1. Break the top of the ampoule, draw up the solvent with a syringe and add the solvent to the powder.
2. 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.

A new needle should be used to administer the vaccine.

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