# Nimenrix™

**Meningococcal polysaccharide serogroups A, C, W-135 and Y conjugate vaccine**

## QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (0.5 ml) contains 5 micrograms of polysaccharide for *Neisseria meningitidis* serogroups A[1], C[1], W-135[1] and Y[1].

[1]conjugated to tetanus toxoid carrier protein 44 micrograms

## PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

## CLINICAL PARTICULARS

### Indications

Active immunization of individuals from 12 months of age against invasive meningococcal diseases caused by *Neisseria meningitidis* serogroups A, C, W-135 and Y (see section "*Pharmacodynamics*").

### Dosage and Administration

**Primary vaccination**
A single 0.5 ml dose of the reconstituted vaccine is used for immunization.

**Booster vaccination**
***Nimenrix™*** may be given in subjects who have previously been vaccinated with a plain polysaccharide meningococcal vaccine.
There are no data available in subjects previously vaccinated with a meningococcal C conjugate vaccine.

***Nimenrix™*** should be used in accordance with available official recommendations.

***Nimenrix™*** is for intramuscular injection only, preferably in the deltoid muscle.
In children 12 to 23 months of age, the vaccine may also be administered in the anterolateral part of the thigh. (see sections "*Warnings and Precautions*" and "*Interactions*").

The safety and efficacy of ***Nimenrix™*** in children under 12 months of age has not yet been established. No data are available.

There are limited data in individuals aged > 55 years.

## Contraindications

***Nimenrix™*** should not be administered to subjects with hypersensitivity to the active substances or to any of the excipients contained in the vaccine. (see sections "*Qualitative and quantitative composition*" and "*List of excipients*").

## Warnings and Precautions

***Nimenrix™*** should under no circumstances be administered intravascularly, intradermally or subcutaneously.

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

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

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

Syncope (fainting) can occur following, or even before, any vaccination 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.

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. Clinical relevance of this observation is unknown.

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

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

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

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.

Although ***Nimenrix™*** contains tetanus toxoid, this vaccine does not substitute for tetanus immunisation.

In toddlers, persistence of antibodies has been evaluated for up to 5 years after vaccination. Similar to the monovalent Men C comparator, a decline in antibody titres over time has been observed. Although the clinical relevance of the waning antibody titres is unknown, in individuals vaccinated as toddlers and remaining at high risk of exposure to meningococcal disease caused by serogroups A, C, W-135 and Y, a booster dose might be considered (see section "*Pharmacodynamic Effects*").

A more rapid waning of serum bactericidal antibody titres against MenA than for other groups (C, W-135, Y), has been observed when using human complement in the assay (see section "*Pharmacodynamic Effects*"). In individuals expected to be at particular risk of exposure to MenA and who received a first dose of ***Nimenrix™*** more than one year earlier, consideration may be given to administering a booster dose of ***Nimenrix™***. Available data indicate that a booster dose will elicit an anamnestic immune response to all four meningococcal serogroups in the vaccine. Currently there is very limited information available on the safety of a booster dose of ***Nimenrix™***.

## Interactions

***Nimenrix™*** can be given concomitantly with any of the following vaccines: hepatitis A (HAV) and hepatitis B (HBV) vaccines, measles - mumps - rubella (MMR) vaccine, measles - mumps - rubella - varicella (MMRV) vaccine, 10-valent pneumococcal conjugate vaccine or unadjuvanted seasonal influenza vaccine. ***Nimenrix™*** can also be given concomitantly with combined diphtheria - tetanus - acellular pertussis vaccines in the second year of life, including combination DTaP vaccines with hepatitis B, inactivated polio or Haemophilus influenzae type b, such as DTaP-HBV-IPV/Hib vaccine.

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

One month after co-administration with a 10-valent pneumococcal conjugate vaccine, lower Geometric Mean antibody Concentrations (GMCs) and opsonophagocytic assay

(OPA) antibody GMTs were observed for one pneumococcal serotype (18C conjugated to tetanus toxoid carrier protein). Clinical relevance of this observation is unknown. There was no impact of co-administration on the other nine pneumococcal serotypes.

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

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

## Pregnancy and Lactation

There is limited experience with use of ***Nimenrix™*** in pregnant women. Animal studies with ***Nimenrix™*** do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryo/foetal development, parturition or post-natal development (see section "*Pre-clinical safety data*").

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

The safety of ***Nimenrix™*** when administered to breast-feeding women has not been evaluated. It is unknown whether ***Nimenrix™*** is excreted in human breast milk. ***Nimenrix™*** should only be used during breast-feeding when the possible advantages outweigh the potential risks.

## 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.

## Adverse Reactions

The safety profile presented below is based on a pooled analysis in more than 9,000 subjects who have been vaccinated with one dose of ***Nimenrix™*** in clinical studies.

Adverse reactions reported are listed according to the following frequency:

| | |
|---|---|
| Very common | ≥ 1/10 |
| Common | ≥ 1/100 to < 1/10 |
| Uncommon | ≥ 1/1000 to < 1/100 |
| Rare | ≥ 1/10000 to < 1/1000 |
| Very rare | < 1/10000 |

Not known (cannot be estimated from the available data)

| **System Organ Class** | **Frequency** | **Adverse reactions** |
|---|---|---|
| **Clinical trials** | | |
| Metabolism and nutrition disorders | Very common | Appetite lost |
| Psychiatric disorders | Very | Irritability |

| | | |
|---|---|---|
| | common | |
| | Uncommon | Insomnia, crying |
| Nervous system disorders | Very common | Drowsiness, headache |
| | Uncommon | Hypoaesthesia, dizziness |
| Gastrointestinal disorders | Common | Gastrointestinal symptoms (including diarrhoea, vomiting and nausea) |
| Skin and subcutaneous tissue disorders | Uncommon | Pruritus, rash |
| Musculosckeletal and connective tissue disorders | Uncommon | Myalgia, pain in extremity |
| General disorders and administration site conditions | Very common | Fever, swelling, pain and redness at injection site, fatigue |
| | Common | Injection site haematoma |
| | Uncommon | Malaise, injection site reaction (including induration, pruritus, warmth, anaesthesia) |
| **Post-marketing Data** | | |
| General disorders and administration site conditions | Rare | Extensive limb swelling at the injection site, frequently associated with erythema, sometimes involving the adjacent joint or swelling of the entire injected limb |

In a separate study a single dose of ***Nimenrix™*** was administered to 274 individuals aged 56 years and older. All adverse reactions reported in this study were already observed in younger age groups.

## Overdose

No cases of overdose have been reported.

# PHARMACOLOGICAL PROPERTIES

## Pharmacodynamics

Pharmacotherapeutic group: bacterial vaccines, ATC code J07AH08

### Mechanism of Action

Anti-capsular meningococcal antibodies protect against meningococcal diseases via complement mediated bactericidal killing. ***Nimenrix™*** induces the production of bactericidal antibodies against capsular polysaccharides of serogroups A, C, W-135 and Y when measured by assays using either rabbit complement (rSBA) or human complement (hSBA). By conjugating capsular polysaccharide to a protein carrier that contains T-cell epitopes, meningococcal conjugate vaccines like ***Nimenrix™*** change the nature of immune response to capsular polysaccharide from T-cell independent to T-cell dependent.

### Pharmacodynamic Effects

The immunogenicity of one dose of ***Nimenrix™*** has been evaluated in more than 8,000 subjects aged ≥ 12 months.

Vaccine efficacy was inferred from the demonstration of immunologic non inferiority (based mainly on comparing proportions with rSBA titres at least 1:8) to licensed meningococcal vaccines. Immunogenicity was measured by using rSBA or hSBA which are biomarkers for protective efficacy against meningococcal groups A, C, W-135 and Y.

The vaccine response was defined in subjects aged ≥ 2 years 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)

**Vaccine immunogenicity**

Immunogenicity in toddlers aged 12-23 months

In clinical studies MenACWY-TT-039 and MenACWY-TT-040, the immune response to vaccination with either ***Nimenrix™*** or a licensed meningococcal C-$CRM_{197}$ conjugate (MenC-CRM) vaccine was evaluated.

***Nimenrix™*** elicited a bactericidal antibody response against the four groups, with a response against group C that was comparable to the one elicited by the licensed MenC-CRM vaccine in term of rSBA titres ≥8 (Table 1).

Table 1: Bactericidal antibody responses (rSBA*) in toddlers aged 12-23 months

| Group | Response to | Study MenACWY-TT-039 rSBA(1) | | | Study MenACWY-TT-040 rSBA(2) | | |
|---|---|---|---|---|---|---|---|
| | | N | ≥8 | GMT | N | ≥8 | GMT |
| A | ***Nimenrix™*** | 354 | 99.7% | 2205 | 183 | 98.4% | 3170 |
| C | ***Nimenrix™*** | 354 | 99.7% | 478 | 183 | 97.3% | 829 |
| | MenC-CRM vaccine | 121 | 97.5% | 212 | 114 | 98.2% | 691 |
| W-135 | ***Nimenrix™*** | 354 | 100% | 2682 | 186 | 98.4% | 4022 |
| Y | ***Nimenrix™*** | 354 | 100% | 2729 | 185 | 97.3% | 3168 |

The analysis of immunogenicity was conducted on the according-to-protocol (ATP) cohorts for immunogenicity.
(1) blood sampling performed 42 to 56 days post vaccination
(2) blood sampling performed 30 to 42 days post vaccination
* tested at GSK laboratories

In the study MenACWY-TT-039, the serum bactericidal activity was also measured using human serum as the source of complement (hSBA) as a secondary endpoint (Table 2).

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

| Group | Response to | N | Study MenACWY-TT-039 hSBA(1) |
|---|---|---|---|

| | | | ≥8 | GMT |
|---|---|---|---|---|
| A | ***Nimenrix™*** | 338 | 77.2% | 19.0 |
| C | ***Nimenrix™*** | 341 | 98.5% | 196 |
| | MenC-CRM vaccine | 116 | 81.9% | 40.3 |
| W-135 | ***Nimenrix™*** | 336 | 87.5% | 48.9 |
| Y | ***Nimenrix™*** | 329 | 79.3% | 30.9 |

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

Immunogenicity in children aged 2-10 years

In two comparative studies conducted in subjects aged 2-10 years, one group of subjects received a dose of ***Nimenrix™*** and a second group a dose of either a licensed MenC-CRM vaccine (study MenACWY-TT-081) or the licensed GlaxoSmithKline Biologicals' plain polysaccharide meningococcal group A, C, W-135, Y (ACWY-PS) vaccine (study MenACWY-TT-038 ) as comparator.

In the MenACWY-TT-038 study, ***Nimenrix™*** was demonstrated to be non-inferior to the licensed ACWY-PS vaccine in terms of vaccine response to the four groups (A, C, W-135 and Y) (Table 3).

Table 3: 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)

| Group | ***Nimenrix™*** | | | ACWY-PS vaccine | | |
|---|---|---|---|---|---|---|
| | N | VR | GMT | N | VR | GMT |
| A | 594 | 89.1% | 6343 | 192 | 64.6% | 2283 |
| C | 691 | 96.1% | 4813 | 234 | 89.7% | 1317 |
| W-135 | 691 | 97.4% | 11543 | 236 | 82.6% | 2158 |
| Y | 723 | 92.7% | 10825 | 240 | 68.8% | 2613 |

The analysis of immunogenicity was conducted on ATP cohort for immunogenicity.
VR: vaccine response
* tested at GSK laboratories

In the MenACWY-TT-081 study, ***Nimenrix™*** (N=268) was demonstrated to be non-inferior to another licensed MenC-CRM vaccine (N=92) in terms of vaccine response to the Men C group (94.8% and 95.7% respectively), GMTs were lower for the ***Nimenrix™*** group (2795) versus the MenC-CRM vaccine (5292).

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.

In both adolescents and adults, ***Nimenrix™*** was demonstrated to be immunologically non-inferior to the ACWY-PS vaccine in terms of vaccine response. The response to

the four meningococcal groups elicited by ***Nimenrix™*** was either similar or higher than the one elicited by the ACWY-PS vaccine (Table 4).

Table 4: 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) | Group | ***Nimenrix™*** | | | ACWY-PS vaccine | | |
|---|---|---|---|---|---|---|---|
| | | N | VR | GMT | N | VR | GMT |
| Study MenACWY-TT-036 (11-17 years) | A | 553 | 85.4% | 5928 | 191 | 77.5% | 2947 |
| | C | 642 | 97.4% | 13110 | 211 | 96.7% | 8222 |
| | W-135 | 639 | 96.4% | 8247 | 216 | 87.5% | 2633 |
| | Y | 657 | 93.8% | 14086 | 219 | 78.5% | 5066 |
| Study MenACWY-TT-035 (18-55 years) | A | 743 | 80.1% | 3625 | 252 | 69.8% | 2127.2 |
| | C | 849 | 91.5% | 8866 | 288 | 92.0% | 7371.2 |
| | W-135 | 860 | 90.2% | 5136 | 283 | 85.5% | 2461.3 |
| | Y | 862 | 87.0% | 7711 | 288 | 78.8% | 4314.3 |

The analysis of immunogenicity was conducted on ATP cohorts for immunogenicity.
VR: vaccine response
* tested at GSK laboratories

In a descriptive study (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), ***Nimenrix™*** was immunogenic, with a vaccine response rate ≥ 63.4%.The percentage of subjects with rSBA titres ≥128 before vaccination ranged from 45% (MenC) to 62% (MenY). Overall, at one month post-vaccination the percentage of vaccines with rSBA titres ≥128 ranged from 93% (MenC) to 97% (MenY). In the subgroup aged >65 years the percentage of vaccines with rSHAB titres ≥ 128 at one month post-vaccination ranged from 90% (MenA) to 97% (MenY).

**Persistence of immune response**

The persistence of the immune response elicited by ***Nimenrix™*** was evaluated up to 48 months after vaccination in subjects aged 12 months to 55 years.

For all groups (A, C, W-135, Y), the persistence of the antibodies elicited by ***Nimenrix™*** was similar or higher than those induced by the licensed meningococcal vaccines [i.e. MenC-CRM vaccine in subjects aged 12-23 months, licensed quadrivalent meningococcal diphtheria toxoid (DT) conjugate (ACWY-DT) vaccine in subjects aged 11-25 years and ACWY-PS vaccine in subjects older than 2 years of age] (Tables 5 to 9).

In contrast to the observed rSBA-MenA persistence, across age groups, there was a more rapid waning (as measured at 12 months post-dose onwards) of serum bactericidal antibody titres against MenA than against other groups (C, W-135, Y) when using human complement in the assay (Tables 5, 6, 7 and 9). This rapid waning of hSBA-MenA antibodies has also been observed with other meningococcal vaccines. The clinical relevance of the rapid waning of hSBA-MenA antibody titres is unknown (see section "*Warnings and Precautions*").

Persistence of immune response in toddlers aged 12-23 months

In children vaccinated at toddler age, the persistence of the immune response was evaluated by rSBA and hSBA up to 4 years in study MenACWY-TT-048 (Table 5) and up to 5 years in study MenACWY-TT-032 (Table 6).

Table 5: 4 years persistence data in toddlers aged 12-23 months at vaccination (study MenACWY-TT-048)

| Group | Response to | Time-point (Year) | rSBA* | | | hSBA** | | |
|---|---|---|---|---|---|---|---|---|
| | | | N | ≥8 | GMT | N | ≥8 | GMT |
| A | ***Nimenrix™*** | 3 | 262 | 59.9% | 19.3 | 251 | 35.9% | 5.8 |
| | | 4 | 224 | 74.1% | 107 | 198 | 28.8% | 4.9 |
| C | ***Nimenrix™*** | 3 | 262 | 35.9% | 9.8 | 253 | 78.3% | 37.8 |
| | | 4 | 225 | 40.4% | 12.3 | 209 | 73.2% | 32.0 |
| | MenC-CRM vaccine | 3 | 46 | 13.0% | 5.7 | 31 | 41.9% | 6.2 |
| | | 4 | 45 | 35.6% | 13.5 | 32 | 46.9% | 11.3 |
| W-135 | ***Nimenrix™*** | 3 | 261 | 49.8% | 24.9 | 254 | 82.3% | 52.0 |
| | | 4 | 225 | 49.3% | 30.5 | 165 | 80.6% | 47.1 |
| Y | ***Nimenrix™*** | 3 | 262 | 53.8% | 22.3 | 250 | 72.0% | 33.2 |
| | | 4 | 225 | 58.2% | 36.2 | 130 | 65.4% | 29.8 |

The analysis of immunogenicity was conducted on ATP cohort for persistence adapted for each time-point.
*rSBA testing performed at Public Health England (PHE) laboratories in UK
** tested at GSK laboratories

Table 6: 5 years persistence data in toddlers aged 12-23 months at vaccination (study MenACWY-TT-032)

| Group | Response to | Time-point (Year) | rSBA* | | | hSBA** | | |
|---|---|---|---|---|---|---|---|---|
| | | | N | ≥8 | GMT | N | ≥8 | GMT |
| A | ***Nimenrix™*** | 4 | 45 | 64.4% | 35.1 | 44 | 52.3% | 8.8 |
| | | 5 | 49 | 73.5% | 37.4 | 45 | 35.6% | 5.2 |
| C | ***Nimenrix™*** | 4 | 45 | 97.8% | 110 | 45 | 97.8% | 370 |
| | | 5 | 49 | 77.6% | 48.9 | 48 | 91.7% | 216 |
| | MenC-CRM vaccine | 4 | 10 | 80.0% | 137 | 10 | 70.0% | 91.9 |
| | | 5 | 11 | 63.6% | 26.5 | 11 | 90.9% | 109 |
| W-135 | ***Nimenrix™*** | 4 | 45 | 60.0% | 50.8 | 45 | 84.4% | 76.9 |
| | | 5 | 49 | 34.7% | 18.2 | 46 | 82.6% | 59.7 |
| Y | ***Nimenrix™*** | 4 | 45 | 62.2% | 44.9 | 41 | 87.8% | 74.6 |
| | | 5 | 49 | 42.9% | 20.6 | 45 | 80.0% | 70.6 |

Persistence of immunogenicity was analysed using the year 5 ATP cohort. A selection bias mainly due to revaccination of subjects with MenC rSBA titers <8 and their exclusion from subsequent timepoint(s) may have led to and overestimation of the titers.

*rSBA testing performed at PHE laboratories in UK
** tested at GSK laboratories

Persistence of immune response in children aged 6-10 years

In study MenACWY-TT-028, the persistence of the immune response was evaluated by hSBA 1 year after vaccination in children 6-10 years of age primed in study MenACWY-TT-027 (Table 7).

Table 7: 1 month post-vaccination and 1 year persistence data (hSBA*) in children 6-10 years of age

| Group | Response to | 1 month post-vaccination | | | 1 year persistence | | |
|---|---|---|---|---|---|---|---|
| | | N | ≥8 | GMT | N | ≥8 | GMT |
| A | ***Nimenrix™*** | 105 | 80.0 % | 53.4 | 104 | 16.3% | 3.5 |
| | ACWY-PS | 35 | 25.7% | 4.1 | 35 | 5.7% | 2.5 |
| C | ***Nimenrix™*** | 101 | 89.1% | 156 | 105 | 95.2% | 129 |
| | ACWY-PS | 38 | 39.5% | 13.1 | 31 | 32.3% | 7.7 |
| W-135 | ***Nimenrix™*** | 103 | 95.1% | 133 | 103 | 100% | 257 |
| | ACWY-PS | 35 | 34.3% | 5.8 | 31 | 12.9% | 3.4 |
| Y | ***Nimenrix™*** | 89 | 83.1% | 95.1 | 106 | 99.1% | 265 |
| | ACWY-PS | 32 | 43.8% | 12.5 | 36 | 33.3% | 9.3 |

The analysis of immunogenicity was conducted on ATP cohort for persistence.
* tested at GSK laboratories

Persistence of immune response in adolescents aged 11-17 years

In study MenACWY-TT-043, the persistence of the immune response was evaluated up to 4 years after vaccination in adolescents primed in study MenACWY-TT-036 (Table 8). See Table 4 for primary results in this study.

Table 8: 4 years persistence data (rSBA*) in adolescents aged 11-17 years at vaccination

| Group | ***Time-point (Year)*** | ***Nimenrix™*** | | | ACWY-PS vaccine | | |
|---|---|---|---|---|---|---|---|
| | | N | ≥8 | GMT | N | ≥8 | GMT |
| A | 3 | 449 | 92.9% | 448 | 150 | 82.7% | 206 |
| | 4 | 391 | 90.3% | 387 | 130 | 80.8% | 174 |
| C | 3 | 449 | 91.1% | 371 | 150 | 86.0% | 390 |
| | 4 | 390 | 94.1% | 378 | 130 | 86.9% | 364 |
| W-135 | 3 | 449 | 82.0% | 338 | 150 | 30.0% | 16.0 |
| | 4 | 390 | 77.2% | 210 | 130 | 26.9% | 11.7 |
| Y | 3 | 449 | 93.1% | 740 | 150 | 58.0% | 69.6 |
| | 4 | 389 | 89.5% | 533 | 130 | 48.5% | 49.8 |

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

Persistence of immune response in adolescents and adults aged 11-25 years evaluated by hSBA

In study MenACWY-TT-059, the persistence of the immune response was evaluated by hSBA 1 and 3 years after vaccination in adolescents and adults 11-25 years of age primed in study MenACWY-TT-052.

For all groups (A, C, W-135, Y), the persistence of the antibodies elicited by ***Nimenrix™*** was similar or higher than those induced by the ACWY-DT vaccine (Table 9).

Table 9: 1 month post-vaccination and 1 and 3 years persistence data in adolescents and adults 11-25 years of age evaluated by hSBA*

| Group | Response to | Month 1 | | | Year 1 | | | Year 3 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | N | ≥8 | GMT | N | ≥8 | GMT | N | ≥8 | GMT |
| A | ***Nimenrix™*** | 356 | 82.0% | 58.7 | 350 | 29.1% | 5.4 | 316 | 37.3% | 6.2 |
| | ACWY-DT | 108 | 73.1% | 41.3 | 112 | 31.3% | 6.0 | 79 | 48.1% | 10.0 |
| C | ***Nimenrix™*** | 359 | 96.1% | 532 | 336 | 94.9% | 172 | 319 | 93.1% | 119 |
| | ACWY-DT | 114 | 99.1% | 320 | 105 | 73.3% | 46.7 | 81 | 81.5% | 54.4 |
| W-135 | ***Nimenrix™*** | 334 | 91.0% | 117 | 327 | 98.5% | 197 | 323 | 95.4% | 144 |
| | ACWY-DT | 97 | 75.3% | 71.9 | 108 | 75.9% | 49.5 | 80 | 85.0% | 79.4 |
| Y | ***Nimenrix™*** | 364 | 95.1% | 246 | 356 | 97.8% | 272 | 321 | 96.0% | 209 |
| | ACWY-DT | 112 | 81.3% | 104 | 113 | 86.7% | 101 | 80 | 88.8% | 145 |

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

**Immune memory**

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

One month after the challenge dose, the GMTs elicited by the subjects primed with ***Nimenrix™*** increased by 6.5 to 8 fold for groups A, C, W-135 and Y and indicate that ***Nimenrix™*** induces immune memory to groups A, W-135 and Y. The post-challenge rSBA-MenC GMT was similar in both study groups, indicating that ***Nimenrix™*** induces an analogous immune memory to group C as the licensed MenC-CRM vaccine (Table 10).

Table 10: Immune response (rSBA*) 1 month after a challenge vaccination in subjects primed with ***Nimenrix™*** or a MenC-CRM vaccine at the age of 12 to 14 months

| Group | Response to | Pre-challenge | | Post-challenge | |
|---|---|---|---|---|---|
| | | N | GMT | N | GMT |
| A | ***Nimenrix™*** | 32 | 544 | 25 | 3222 |
| C | ***Nimenrix™*** | 31 | 174 | 32 | 5966 |
| | MenC-CRM vaccine | 28 | 34.4 | 30 | 5265 |
| W-135 | ***Nimenrix™*** | 32 | 644 | 32 | 11058 |
| Y | ***Nimenrix™*** | 32 | 440 | 32 | 5737 |

The analysis of immunogenicity was conducted on ATP cohort for immunogenicity.
* tested at GSK laboratories

**Booster response**

In study MenACWY-TT-048, a booster response was evaluated in children vaccinated 4 years earlier (at toddler age) in study MenACWY-TT-039 (Table 2). Children were primed and boosted with the same vaccine: either ***Nimenrix™*** or a MenC-CRM vaccine. A robust increase in rSBA and hSBA GMTs was observed from pre-booster dose to one month post-booster dose of ***Nimenrix™*** (Table 11).

Table 11: Pre-booster and 1 month post-booster data in children vaccinated either with ***Nimenrix™*** or MenC-CRM vaccine 4 years earlier (at toddler age)

| Group | Response to | Time-point | rSBA* | | | hSBA** | | |
|---|---|---|---|---|---|---|---|---|
| | | | N | ≥8 | GMT | N | ≥8 | GMT |
| A | ***Nimenrix™*** | Pre-Booster | 212 | 74.5% | 112 | 187 | 28.9% | 4.8 |
| | | Post-Booster | 214 | 100% | 7173 | 202 | 99.5% | 1343 |
| C | ***Nimenrix™*** | Pre-Booster | 213 | 39.9% | 12.1 | 200 | 73.0% | 31.2 |
| | | Post-Booster | 215 | 100% | 4512 | 209 | 100% | 15831 |
| | MenC-CRM vaccine | Pre-Booster | 43 | 37.2% | 14.3 | 31 | 48.4% | 11.9 |
| | | Post-Booster | 43 | 100% | 3718 | 33 | 100% | 8646 |
| W-135 | ***Nimenrix™*** | Pre-Booster | 213 | 48.8% | 30.2 | 158 | 81.6% | 48.3 |
| | | Post-Booster | 215 | 100% | 10950 | 192 | 100% | 14411 |
| Y | ***Nimenrix™*** | Pre-Booster | 213 | 58.2% | 37.3 | 123 | 65.9% | 30.2 |
| | | Post-Booster | 215 | 100% | 4585 | 173 | 100% | 6775 |

The analysis of immunogenicity was conducted on the booster ATP cohort for immunogenicity.
*rSBA testing performed at PHE laboratories in UK
** tested at GSK laboratories

**Immunogenicity in subjects previously vaccinated with a plain polysaccharide meningococcal vaccine**

In study MenACWY-TT-021 conducted in subjects aged 4.5-34 years, the immunogenicity of ***Nimenrix™*** administered between 30 and 42 months after vaccination with the ACWY-PS vaccine was compared to the immunogenicity of ***Nimenrix™*** administered to age-matched subjects who had not been vaccinated with any meningococcal vaccine in the preceding 10 years. The rSBA GMTs were significantly lower in the subjects who had received a dose of ACWY-PS vaccine 30-42 months prior to ***Nimenrix™*** (Table 12). Clinical relevance of this observation is unknown since all subjects achieved rSBA titres ≥ 8 for each group (A, C, W-135, Y).

Table 12: Immune response (rSBA*) 1 month after ***Nimenrix™*** vaccination in subjects according to their meningococcal vaccine history

| Group | Subjects vaccinated 30 to 42 months previously with ACWY-PS | | | Subjects who had not received a meningococcal vaccine in the preceding 10 years | | |
|---|---|---|---|---|---|---|
| | N | ≥8 | GMT | N | ≥8 | GMT |
| A | 146 | 100% | 6869 | 69 | 100% | 13015 |
| C | 169 | 100% | 1946 | 75 | 100% | 5495 |
| W-135 | 169 | 100% | 4636 | 75 | 100% | 9078 |
| Y | 169 | 100% | 7800 | 75 | 100% | 13895 |

The analysis of immunogenicity was conducted on ATP cohort for immunogenicity.
* tested at GSK laboratories

### Pharmacokinetics

Not relevant for vaccines.

### Clinical Studies

See section "*Pharmacodynamics*".

### Pre-clinical 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.

## PHARMACEUTICAL PARTICULARS

### List of Excipients

Powder: sucrose, trometamol.
Solvent: sodium chloride, water for injections.

### Incompatibilities

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

### Shelf Life

The expiry date is indicated on the label and packaging.

### Special Precautions for Storage

- Store in a refrigerator (2°C – 8°C)
- The solvent may also be stored at ambient temperature (25°C)
- Do not freeze
- Protect from light

### Nature and Contents of Container

- Powder in a vial containing 1 dose (type I glass) with a stopper (butyl rubber) and 0.5 ml of solvent for 1 dose in a pre-filled syringe with a stopper (butyl rubber). Pack sizes of 1 and 10 with or without needles.

- Powder in a vial containing 1 dose (type I glass) with a stopper (butyl rubber) and 0.5 ml of solvent for 1 dose in an ampoule (type I glass).
  Pack sizes of 1, 10 and 100

  The powder is white. The solvent is clear and colourless.

## Instructions for Use/Handling

**Before reconstitution:**

Instructions for reconstitution of the vaccine with solvent presented in ampoules

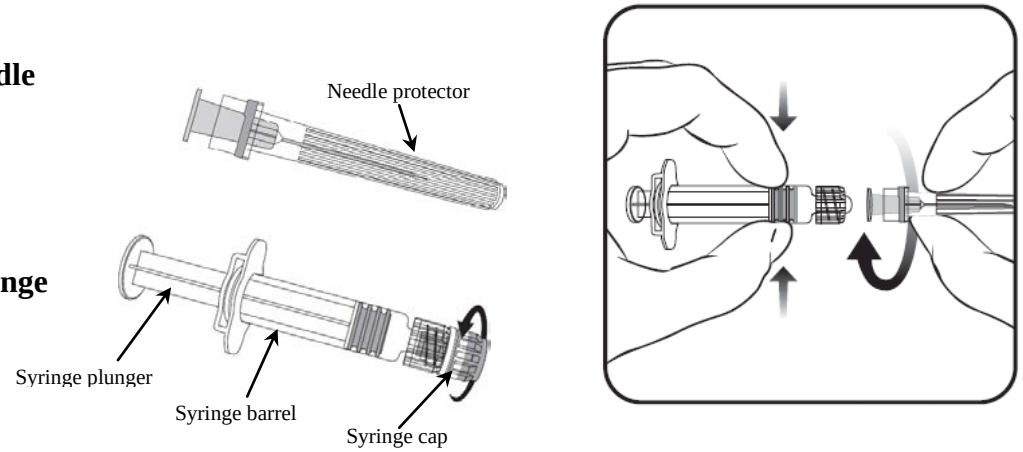
***Nimenrix™*** must be reconstituted by adding the entire content of the ampoule of solvent to the vial containing the powder. To do so, break the top of the ampoule, draw up the solvent with a syringe and add the solvent to the powder. The mixture should be well shaken until the powder is completely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

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 drawing. However, the syringe provided with ***Nimenrix™*** might be slightly different than the syringe described in the drawing.

**Needle**

**Syringe**




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.

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.

**After reconstitution:**
The reconstituted vaccine is a clear colourless solution.
The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of physical aspect prior to administration. In the event of either being observed, discard the vaccine.

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

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

Not all presentations are available in every country.

***Nimenrix* is a trademark of the GSK group of companies**

**Version number: GDS006/IPI005SI/ Date of issue: 05 November 2014**



**Manufacturer:**
**GlaxoSmithKline Biologicals s.a.**
**89, rue de l'Institut - 1330 Rixensart**
**Belgium**

[GSK Logo]