**Unit: Technical Assessment Unit**

# Public assessment report for biological products

***(Nimenrix)***

## Administrative information:

| | |
|---|---|
| Trade name of the medicinal product: | Nimenrix |
| INN (or common name) of the active substance(s): | Neisseria meningitidis group A polysaccharid<br><br>Neisseria meningitidis group C polysaccharide<br><br>Neisseria meningitidis group W-135 polysaccharide<br><br>Neisseria meningitidis group Y polysaccharide<br><br>conjugated to tetanus toxoid carrier protein |
| Manufacturer of the finished product | GlaxoSmithKline Biologicals S.A., 89, rue de l'Institut, B-1330 Rixensart - Belgium<br><br>GlaxoSmithKline Biologicals S.A., Parc de la Noire Epine, 20 rue Fleming, B-1300 Wavre - Belgium |
| Marketing Authorization holder | GlaxoSmithKline Biologicals S.A., 89, rue de l'Institut, B-1330 Rixensart - Belgium |
| Applied Indication(s): | The vaccine is expected to trigger the immune memory and induce the production of antibodies against Neisseria meningitides serogroup A, C. W and Y. |
| Pharmaceutical form(s) and strength(s): | Powder and solvent for solution for injection<br><br>After reconstitution, each 0.5ml (1 dose) contains: |

| | |
|---|---|
| | Neisseria meningitidis group A polysaccharide 5 µg<br>Neisseria meningitidis group C polysaccharide 5 µg<br>Neisseria meningitidis group W-135 polysaccharide 5 µg<br>Neisseria meningitidis group Y polysaccharide 5 µg<br>conjugated to tetanus toxoid carrier protein 44 µg |
| Route of administration | Intramuscular injection only |
| Type of registration (EMA/FDA – Local) | Imported |

**List of abbreviations**

PS-TT :Polysaccharide Tetanus Toxoid
IPC: In-Process control

Men PS-TT bulks: Meningococcal Polysaccharide- tetanus toxoid bulks

TRS: Technical Report Series

Ph. Eur: European Pharmacopeia

AH: Adipic acid dihydrazide

CI: Confidence Interval

ELISA: Enzyme-Linked Immunosorbent Assay

GMT: Geometric Mean Titre

IM: Intramuscular(ly)

IV: Intravenous(ly)

MenC: Meningococcal Group C

MenA: Meningococcal Group A

MenW-135: Meningococcal Group W-135

MenY: Meningococcal Group Y

MenCC: Meningococcal Group C Conjugate Vaccine

NZW rabbits: New Zealand White rabbits

rSBA: Serum Bactericidal Assay using Rabbit Complement

hSBA: Serum Bactericidal Assay using Human Complement

PS: Polysaccharide

SPC: Summary of Product Characteristics

TT: Tetanus Toxoid

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1. **Quality aspects:**

1.2.1 Introduction

Nimenrix (Meningococcal group A, C, W-135 and Y conjugate vaccine) is presented by GlaxoSmithKline Biologicals. It consists of four polysaccharides conjugated to a tetanus toxoid protein carrier.

The PS-TT conjugates consist of the purified polysaccharides of Neisseria meningitides serogroups A, C, W135 and Y respectively, conjugated to tetanus toxoid as a carrier protein. The vaccine's code name is MenACWY-TT. The tradename is "Nimenrix".

MenACWY-TT is a non adsorbed freeze-dried preparation presented as monodose vials to be

Re-constituted with a diluent (saline solution). The diluent is presented in glass ampoules or in glass syringes. The final reconstituted vaccine is preservative free and is presented as a liquid monodose for intramuscular injection.

It's found as powder (white in color) in a vial (type I glass) with a stopper (butyl rubber) and solvent (clear colourless- saline solution) in an ampoule (type I glass).

3.2.S Drug Substance (Active ingredient)

**General information**

MenACWY-TT is tetravalent conjugated polysaccride vaccine that consists of polysaccharide of Neisseria meningitidis serogroups A.C. W 135, Y conjugated to carrier protein tetanus toxoid (TT).

**Manufacture, process controls and characterization:**

| Manufacturer | Responsibilties |
|---|---|
| GlaxoSmithKline Biologicals S.A.<br>Parc de la Noire Epine<br>Rue de Flemming, 20<br>B-1300 Wavre<br>Belgium | *N.meningitidis* serogroup A,C,W,Y purified polysaccharide MenA bulk manufacturing and testing |
| | Purified tetanus toxoid testing |
| | Purified ultrafiltered tetanus toxoid Testing |
| | Conjugated *N.meningitidis* group A,C,W,Y purified polysaccharide testing |
| GlaxoSmithKline Biologicals Kft.<br>Táncsics Mihály út. 82<br>2100 Gödöllö<br>Hungary | Purified tetanus toxoid bulk Manufacturing |
| | Purified tetanus toxoid testing |
| GlaxoSmithKline Biologicals S.A.<br>Rue de l'Institut, 89<br>B-1330 Rixensart<br>Belgium | Purified tetanus toxoid testing |
| | Purified and ultrafiltered tetanus toxoid Manufacturing |
| | Conjugated *N.meningitidis* group A,C,W,Y purified polysaccharide manufacture |

**Description of Manufacturing Process and Process Controls.**

The detailed manufacturing process is mentioned in the MA file along with flow diagram highlighting the process steps with their IPCs.

-The DS is manufactured through the following steps:

1-Manifacturing process of purified polysaccharide bulk

2-Mnufacturing of purified TT

3-Manufacturing of the polysaccharide tetanus toxoid conjugate(Men *A -TT* and Men *C-TT)*

4- Manufacturing of the polysaccharide tetanus toxoid conjugate(Men *W -TT* and Men *Y-TT*)
The steps of each process are described in details in MA file

**Control of Materials.**

-List of strains used in the manufacturing process is provided along with quality control testing and specification .

-- information regarding the used cell line & cell banking is mentioned in detail in the MA file.

-- Biologically-sourced materials (their suitability for intended use including clearance or control of adventitious agents), Their specific use in the process and TSE/BSE risk evaluation are described in the dossier.

**Controls of Critical Steps and Intermediates**.

-Critical process steps and critical process parameters are mentioned in the manufacturing process .

-The process controls selected for each critical manufacturing step and the acceptance criteria are provided in the MA file .

**Process Validation**

**2.2.5 Process Validation and/or Evaluation.**

The process validation activities were carried out at various stages of the bulk purified diphtheria toxoid manufacture and were submitted in the CTD

-**Manufacturing Process Development.**

-The developmental history of the manufacturing process is sufficiently describing the whole changes made to the DS manufacturing process with proper justification.

- Detailed description for each step development is mentioned in the MA file.

- Relevant information on DS batches manufactured during development, such as the batch number (and sub sequential drug product batch numbers), manufacturing date, scale, and use (e.g., stability, nonclinical, reference material) in relation to the change, are presented.

**Characterization.**

-Physicochemical, biological &immunological characterization has been well presented.

-Characterization tests are fully described in the MA file.

-The manufacturer presented clearance data for several identified impurities.

-The applied methods for detection of impurities have been described and full validations of these methods have been presented in the dossier.

**Specification**

Specifications are in line with WHO , Ph. Eur and in-house Specifications.

**Reference Standards or Materials.**

-Certificate of analysis & instructions of use for reference standards are presented.

- Reference materials used in QC testing of MenACWY-TT conjugated bulk together with supportive information on their stability is provided.

**Container closure system**

-The purified PS-TT conjugate bulks are stored in glycol-modified polyethylene terephtalate (PETG) vials. The containers are closed with polypropylene screw caps. The containers are supplied clean and sterile. The closure system is of pharmaceutical grade. The compatibility between PS-TT bulk and primary container/closure materials is retrospectively **demonstrated** through real-time stability studies.

**Stability of drug substance**

-Based on the data, the manufacture proposes a shelf life claim of 6 months at +2/+8°C for MenAAH-TTconjugates, 12 months at +2/+8°C for MenCAH-TT conjugates, and 24 months at +2°C to +8°C for MenY-TT & MenW-TTconjugates.

**3.2.P Drug product:**

**Description and Composition of the Drug Product:**

The GlaxoSmithKline Biologicals' MenACWY-TT is composed of the purified capsular polysaccharides of Neisseria meningitidis types A, C. W and Y, each conjugated to tetanus toxoid at ratios (toxoid to polysaccharide) of approximately 3, 3, 1.5 and 1.3, respectively.

MenACWY-TT is a non adsorbed freeze-dried preparation presented as monodose vials to be reconstituted with a diluent (saline solution). The diluent is presented in glass in glass syringes (monodoses).

The diluent drug product is a 0.9% sodium chloride solution. Sodium chloride and water for injections (WFI)

The final reconstituted vaccine is preservative free and is present as a liquid monodose for intramuscular injection**.**

**- Pharmaceutical Development including brief description on** Components of drug product

The MenACWY-TT vaccine consists of four polysaccharides conjugated to a protein carrier, which are coded MenAAE-TT. MenCAH-TT, MenW-TT and MenY-TT

The PS-TT conjugates consist of the purified polysaccharides of Neisseria meningitidis serogroup A. C. W and Y respectively, conjugated to tetanus toxoid as carrier protein

The compatibility of the drug substances with each other was demonstrated in clinical trials. The compatibility between the drug substances and the excipients is supported by the satisfactory real-time stability data generated at the recommended storage temperature as well as by the satisfactory immune response induced agamst all vaccine antigens.

**Formulation Development**

The product development has been adequately described in the MA file and the rationale for the final formulation is justified .

**- Overages**

A 25% overage is implemented during the manufacturing of the MenACWY-TT final bulk

**- Physicochemical and Biological Properties**

The candidate vaccine is expected to trigger the immune memory and induce the production of antibodies against Neisseria meningitides serogroup A, C. W and Y.

**- Manufacturing Process Development.**

The batch release data obtained on clinical consistency lots as well as the results of real-time stability studies performed show that all batches meet the pre-defined specifications.

**- Container closure system and their compatibility.**

-Glass vials meet Ph. Eur Requirements for "Glass containers for pharmaceutical use" Vaccines, diluents and adjuvants are filled in 3 ml vials. Un coloured glass. (drawn glass. type I).

-Satisfactory details of container closure system have been provided.

-Tests and specifications are presented. Corresponding methods of analysis other than those described in Ph. Eur. are detailed in GSK Bio Method of analysis and presented.

**Manufacture of the drug product:**

**-** Description of manufacturing process and process controls along with manufacturers and responsibilities.

A flow chart of the manufacturing process is presented, including all the steps in the process. The points at which the material enters the process, the critical steps and control points in the process are presented. Intermediate products, final product, the in-process controls, and the critical points are identified.

-The Men ACWY-TT vaccine is manufactured using a validated process under aseptic conditions and in compliance with Good Manufacturing Practice (GMP).

Each manufacturing step is subject to in-process controls and quality assurance measures to ensure product consistency, safety, and efficacy. Critical process parameters are monitored throughout production, and the final product is tested according to approved specifications before release.

**Control of critical steps and intermediates**

There is no intermediate product produced between the formulated final bulk vaccine and the end of the lyophilization process..

In-process controls and monitoring are performed at critical steps of the manufacturing process to ensure process performance and product quality:

All critical steps are carried out under validated conditions, and monitored according to Good Manufacturing Practice (GMP) standards. Process parameters and controls are established to ensure consistent product quality throughout the manufacturing cycle.

**Process validation and / or evaluation.**

**Validation of the process:**

-The process validation for Men ACWY-TT lyophilized vaccine have been demonstrated

-The demonstration of process consistency for at least 3 consecutive batches that show compliance with the pre-established quality specifications.

-The identification and validation of the manufacturing process critical parameters for specific operations.

Data on the process consistency demonstration and on the identification and validation of the manufacturing process critical parameters are presented.

**Product specification:**

The specifications for the routine release of Men ACWY at final bulk and final container levels are described in the file
-Excipients are mentioned in the dossier along with their specifications ,detailed analytical procedures and their references.

**Characterization of impurities.**

-No impurities are specifically generated by formulation and filling processes

**Reference Standards or Materials**

-The reference standards used in the testing of Men ACWY-TT final containers are listed in the submitted file. All reference lots complied with specifications in force at time of release. Batch analysis data for these lots are provided

**Container closure system.**

-Satisfactory details of container closure system have been provided.

**Stability of the drug product.**

-Stability data are presented in the submitted file.
-All results meet the proposed acceptance criteria.
-An expiration date of 36 months at +2 to +8°C is proposed for the MenACWY-TT final container vaccine.
- For commercial vaccine, the expiry date will be calculated based on the production date, which is defined as the date of the first day of filling

**2. Non –clinical aspect:**

Nimenrix® (ACWY-TT) is a Meningococcal group conjugate vaccine that consists of four purified polysaccharides of Neisseria meningitidis serogroups A, C, W135 and Y respectively, conjugated to tetanus toxoid as a carrier protein. Serogroup A and C are conjugated to tetanus toxoid with an adipic dihydrazide (AH) spacer while MenVW-135 and MenY polysaccharides are conjugated directly (3rd generation MenAAHCAHWY-TT). It is indicated for active immunization of individuals from the age of 12 months and above against invasive meningococcal diseases caused by Neisseria meningitides group A, C, W-135 and Y.

Pharmacology: The impact of conjugation of purified PS to TT on the immunogenicity of the meningococcal PS was assessed in mice. The results showed that conjugated PS induces a significantly higher bactericidal response, as compared to plain polysaccharides which are poorly or non-immunogenic. The immunogenicity of the candidate vaccine was also evaluated in NZW

rabbits in three independent studies (as a part of repeat-dose toxicity studies), using each of the three generation vaccines;

· 1st generation MenACWY-TT (no AH spacer was used),

· 2nd generation MenAAHCWY-TT (only Serogroup A is conjugated to TT with AH spacer),

· 3rd generation MenAAHCAHWY-TT (both Serogroup A and C are conjugated to TT with AH spacer).

- Results confirmed that the addition of a spacer to the MenA-TT and MenC-TT conjugates increases their immunogenicity as compared to the same conjugates without spacer, and that this modification has no impact on the immunogenicity of MenW and MenY conjugates. A dose-related response was also observed. Regarding safety pharmacology, MenAAHCAHWY-TT vaccine was examined IM and IV at a dose 63-fold higher than the intended human dose relative to bodyweight. Both IM and IV administration of the candidate vaccine did not produce any treatment-related effects on any recorded CV or respiratory parameters.

Ø Pharmacokinetics: As noted in the WHO Guidelines on Nonclinical Evaluation of Vaccines and EMEA/CPMP Note for Guidance on Preclinical Pharmacological and Toxicological testing of Vaccines (CPMP/SWP/465/95), pharmacokinetics testing is not required for final vaccine formulations.

Ø Toxicology: Repeated dose toxicity studies performed with the third-generation vaccine in rabbits demonstrated no sign of toxicity (i.e. deaths, clinical signs, effects on bodyweight gain), absence of signs of systemic or target organ toxicity and no abnormalities noted at necropsy. Hematological and clinical biochemistry parameters were unaffected by repeated exposure to the vaccine. The results showed good local tolerance with no macroscopic lesions at injection sites. Regarding Reproductive and Developmental Toxicity, IM administration of the third-generation candidate vaccine to female rats twice prior to mating and four times during gestation produced no treatment-related effects on maternal toxicity, fertility, prenatal development (including external, visceral and skeletal abnormalities), or postnatal development of the pups up to 25 days after birth.

Ø Overall conclusion: Pre-clinical studies provide good evidence that the candidate vaccine is safe, well tolerated and immunogenic

3. **Clinical aspect:**

Clinical Efficacy including Immunogenicity

Clinical data demonstrate that Nimenrix (MenACWY-TT) elicits robust immune responses and is non-inferior to comparator vaccines such as Mencevax, Meningitec, and Menjugate across multiple age groups. From the age of 2 years, Nimenrix induces functional antibody titres at least comparable to those generated by the corresponding

polysaccharide vaccines, with most evidence indicating immunological advantages for the conjugate formulation—particularly among younger populations.

In children aged 1–2 years, Nimenrix produced strong rSBA and hSBA responses, with the MenC component comparable to that of licensed MenC conjugate vaccines. When administered at 12–14 months, it successfully induced immune memory. Although anti-MenA hSBA titres declined relatively quickly across all age groups, the clinical relevance of this finding remains uncertain.

Differences observed between ELISA and functional antibody assays likely reflect variations in antibody quality between conjugated and unconjugated vaccines. Importantly, Nimenrix demonstrated booster capability in individuals previously vaccinated with meningococcal vaccines, though the magnitude of response was lower than in vaccine-naïve subjects. A negative correlation between baseline anti-TT antibody levels and post-vaccination responses was noted but did not compromise the overall immunogenicity.

In infants, two doses of Nimenrix generated higher antibody titres and longer persistence compared with a single dose, despite the current indication beginning at 12 months of age. In coadministration studies, non-inferiority was demonstrated with all evaluated vaccines except for minor variations observed with Fluarix (MenA, W-135, Y components) and Synflorix (pneumococcal serotype 18C), which were not considered clinically significant.

Clinical Safety

Across clinical trials, Nimenrix exhibited a favorable safety and tolerability profile. Overall, its safety outcomes were comparable to those of Mencevax, Meningitec, and Menjugate, with only minimal differences reported in two studies (MenACWY-TT-036 and -038).

The most common local reactions included injection site pain (24.1%–39.9%), redness (14.3%– 33.0%), and swelling (11.2%–17.9%). These events were generally mild to moderate and transient, consistent with other conjugate vaccines. While Nimenrix showed slightly higher reactogenicity for some symptoms compared with polysaccharide and MenC conjugate vaccines, no safety concerns were identified.

No serious adverse events were attributed to the vaccine. In co-administration studies, the safety profile remained consistent, and no new safety signals emerged. Minor

immunogenicity variations observed during co-administration did not correlate with any adverse safety outcomes.

Overall Conclusion

Nimenrix (MenACWY-TT) demonstrates high immunogenicity, efficacy, and a well-established safety profile across various age groups. The conjugate nature of the vaccine provides enhanced and sustained immune responses, particularly in younger children, and supports its inclusion in routine immunization programs for the prevention of invasive meningococcal disease caused by serogroups A, C, W-135, and Y

**4. General Conclusion and Recommendations if any:**

Based on the review of CTD modules and other supplementary documents, the product is approved.