Summary of Product Characteristics

1) NAME OF THE MEDICINAL PRODUCT

Meningococcal A conjugate vaccine 5 micrograms, Lyophilized
Brand name- MenAfriVac

2) QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, each dose of 0.5mL contains:
Neisseria meningitidis group A (Strain M1027) polysaccharide ……. 5 µg
Conjugated totetanus toxoid 5-16.5µg
For a full list of excipients see section 6.1
Diluent: Each ampoule contains the diluent with aluminium phosphate as adjuvant (the amount does not exceed 1.25 mg per single human dose) and thiomersal (0.01%) as preservative. The diluent is a white slightly opaque homogeneous suspension presented in a 5 mL ampoule.

3) PHARMACEUTICAL FORM

Lyophilized vaccine for reconstitution with the sterile diluent provided by the manufacturer. White lyophilized mass freely soluble in diluent. After reconstitution with the entire content of the supplied container of diluent, the vaccine is a homogeneous suspension.

4) CLINICAL PARTICULARS

4.1 Therapeutic indication

Active immunization for the protection against invasive meningococcal disease caused by *N. meningitidis* group A in young children aged 3 to 24 months.

4.2 Posology and method of administration

4.2.1 Posology

0.5 mL of the reconstituted vaccine constitutes one dose.
Meningococcal A Conjugate Vaccine 5 µg is recommended for routine immunization ofchildren aged 3 to 24 months.
A single dose of 0.5 mL is recommended.

Persons who have previously received a Meningococcal A polysaccharide containing vaccinecan be vaccinated with Meningococcal A Conjugate Vaccine.

4.2.2 Method of administration

Meningococcal A Conjugate Vaccine 5 micrograms is for intramuscular (IM) use only. It should be administered by deep intramuscular injection, preferably in the deltoid muscle or rightthigh.
The lyophilized vaccine must be reconstituted by adding the entire contents of the supplied

container of diluent to the vaccine vial, by using a sterile needle and sterile syringe. The vaccine pellet should be completely dissolved in the diluent. The vaccine should be inspected visually for any foreign particulate matter prior to administration. In the event of it being observed, the vaccine must be discarded.
A separate sterile syringe and sterile needle should be used for each individual subject to prevent transmission of hepatitis or other infectious agents from one person to another. Needles should be properly disposed of and should not be recapped.
Once the vaccine has been reconstituted, it should be used the same day [preferably immediately but by no means beyond six (6) hours after reconstitution] and only then if the vial has been maintained between 2-8ºC and protected from sunlight. Any opened container remaining at the end of a session should be discarded.

4.2.3 Contraindications

Meningococcal A Conjugate Vaccine 5 µg must not be administered to subjects with known hypersensitivity to any component of the product or to subjects having shown hypersensitivity after previous administration of the vaccine.
It should not be used in subjects with acute infectious diseases and/or ongoing progressive (acute or chronic) illnesses. Any body temperature ≥ 38°C or serious active infection is reason for delaying immunization.

4.2.4 Special warnings and special precautions for use

Before administration of each dose of Meningococcal A Conjugate Vaccine 5 µg to a child, the child's parent or guardian should be questioned about possible adverse events after the previous dose or after a previous dose of a TT-containing vaccine.
If the vaccine is used in infants who are immunosuppressed or who are receiving immunosuppressive therapy, an adequate immune response may not be induced.
As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available. Since anaphylactic, anaphylactoid or other allergic type reactions are theoretically possible following administration of Meningococcal A vaccine, epinephrine (adrenaline) 1:1000 and other drugs such as hydrocortisone injection and chlorpheniramine maleate injection, should be available for immediate treatment if such reaction occurs. For this reason, the vaccinee should remain under medical supervision for 30 minutes after immunization. Prior to an injection of any vaccine all known precautions should be taken to prevent adverse reactions.
The vaccine must not be administered subcutaneously or intravenously; they must not be mixed with other vaccines in the same syringe.
Administration of this vaccine does not substitute for routine tetanus vaccination.

There is no evidence that Meningococcal A Conjugate Vaccine 5 µg can cause meningococcal meningitis. Clinical alertness to the possibility of co-incidental meningitis should be maintained.

4.2.5 Interactions with other medicinal products and other forms of interaction

Following administration of the vaccine to persons receiving chronic immunosuppressive therapy, an adequate immunologic response may not be obtained.
Meningococcal A Conjugate Vaccine 5 µg can be safely and effectively given concomitantly with the other EPI vaccines as recommended.

4.2.6 Pregnancy and lactation
Not applicable.

4.2.7 Effects on ability to drive and use machines
Not applicable.

4.2.8 Undesirable effects
Safety of Meningococcal A Conjugate Vaccine 5 µg has been evaluated in Phase II and Phase III clinical trials, given concomitantly with EPI vaccines. It has been found very safe. The reactogenicity profile of Meningococcal A Conjugate Vaccine 5 µg concomitant with EPI vaccines in infants was shown to be similar to that of concomitantly given EPI vaccines. Local reactions at injection sites of Meningococcal A Conjugate Vaccine 5 µg and EPI vaccines were predominantly mild and transient. Local reactions at the site of injection were observed in less than 11% of infants. There were no significant increases in systemic reactions due to concomitant vaccination of the vaccine compared to the EPI vaccines administered alone.
No clinically significant differences in the frequency or severity of adverse events within 28 days of vaccination were observed among infants receiving Meningococcal A Conjugate Vaccine 5 µg simultaneously with the EPI vaccines compared to EPI vaccines alone, indicating a comparable safety profile. All adverse reactions following immunization were transient and resolved without sequelae.

Frequency of Reactions	Adverse Reactions
Very common (>1:10)	Injection site tenderness, diarrhoea
Common (1:100 and≤1:10)	Induration, fever, loss of appetite, vomiting, lethargy, persistent crying
Rare (>1:1000 and ≤1:100)	Irritability, rash

4.2.9 Overdose
Cases of overdose have not been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic Group: Meningococcal vaccines, ATC Code: J07AH

Field efficacy studies have not been performed; rather the effectiveness of the Meningococcal A Conjugate Vaccine 5 µg is based on its ability to induce levels of bactericidal antibodies not inferior to those induced by the licensed meningococcal polysaccharide conjugate vaccine i.e. MenAfriVac 10 µg. A validated serum bactericidal antibody assay using baby rabbit complement (rSBA) was used to measure the functional antibody titer in human sera to Group A Neisseria meningitidis. Immunological non- inferiority was demonstrated in the target population (young children aged 3 to 24 months) based on the following endpoint: seroconversion defined as a ≥ 4-fold increase in MenA rSBA titers. MenA rSBA titers ≥ 1:8 and ≥ 1:128 were assessed as putative correlates for protection and long-term protection to invasive disease caused by Group A Neisseria meningitidis.

5.1.1 Immunogenicity

The primary serological assay used to assess the immunogenicity of the Meningococcal A Conjugate Vaccine 5 µg was rSBA to measure functional antibody activity. This is in line with the WHO recommendation for the evaluation of meningococcal vaccines.

Vaccine response was defined as seroconversion i.e. as a ≥ four-fold increase in rSBA titre from pre to post vaccination.

Two randomized controlled clinical trials were conducted to evaluate reduced antigenic contents of the vaccine compared to the licensed MenAfriVac 10 µg/dose vaccine. The study results demonstrate that the 5 µg dosage is both safe and immunologically non-inferior to MenAfriVac (10 µg) that has shown to be safe and efficacious in the field and confirm that the selected infant dosage, 5 µg, is indeed non-inferior to MenAfriVac (10 µg) and therefore likely to be as effective when used in infants aged 3 to 24 months.

The first study evaluated reduced antigenic contents of Meningococcal A conjugate vaccine- 5 µg and 2.5 µg polysaccharide A- conjugated to tetanus toxoid in infants aged 14 weeks at time of the first dose, compared to MenAfriVac (10 µg dose). The second study compared the 5 µg polysaccharide A conjugated to tetanus toxoid in infants aged 9 months to MenAfriVac (10 µg). In both trials, study vaccines were concomitantly given with EPI and rubella vaccines as recommended.

Immunogenicity data in infants aged from 14 weeks (first study) to 9 months (second study) at time of first vaccination indicate that Meningococcal A Conjugate Vaccine 5 µg elicits functional immune responses that are similar to those induced by MenAfriVac (10 µg).

In both studies, non-inferiority of Meningococcal A Conjugate Vaccine 5 µg to MenAfriVac (10 µg) was demonstrated in terms of the primary immunogenicity endpoint for subjectswith a seroconversion in MenA rSBA antibody titer.

In the first study, with respect to percentage of subjects with a 4-fold or higher

response inMenA rSBA antibody titer with respect to baseline, non-inferiority of Meningococcal AConjugate Vaccine 5 µg administered in 14 weeks and 9 months of age to MenAfriVac (10 µg) administered in 14 weeks and 9 months of age, concomitantly with EPI vaccines, was demonstrated at 28 days after vaccination up to 24 to 27 months after the second dose. The design of the study provided data on the persistence of antibody.

Findings indicate that a schedule consisting of 2 doses of Meningococcal A Conjugate Vaccine 5 µg given at 14 weeks and 9 months of age was highly immunogenic. One month after the second dose, geometric mean titer (GMT) of MenA rSBA was high (5048.6) for Meningococcal A Conjugate Vaccine 5 µg and significantly greater than that achieved by a single dose of MenAfriVac (10 µg) at 9 months indicating that the first dose of Meningococcal A Conjugate Vaccine 5 µg is effectively priming the immune system. MenA rSBA antibody titers ≥ 1/128 were persisting in 88.1% of subjects in the 5 µg group at the age of 36 months.

In the second study, non-inferiority of 5 µg administered at 9 months of age or administered at 9 months and 15 months of age to MenAfriVac (10 µg) administered in 9 months and 15 months of age, concomitantly with EPI vaccines was established at 28 days after the last vaccine dose. High percentages of subjects developed a 4-fold or higher response in MenA rSBA titer with respect to baseline in all groups.
The Meningococcal A Conjugate Vaccine 5 µg was shown to have an immune response profile over time at least as good as that of MenAfriVac (10 µg), whether administered in a one-or- two-dose schedule. Based on the immune response profile over an extended period of time of the MenAfriVac (10 µg) vaccine when given in a one-dose or two-dose schedule, it is reasonable to predict that the trajectory of immune response of the Meningococcal A Conjugate Vaccine 5 µg will follow a similar trend and that a single dose of this vaccine given from age 9 months onwards will induce sustained antibody levels over time.
It is therefore highly probable that Meningococcal A Conjugate Vaccine 5 µg would be as effective as MenAfriVac (10 µg) to prevent group A meningococcal disease in infants when given as a two dose schedule at the age of 3 months and 9 months, or as one dose schedule given from the age of 9 to 24 months.

Conclusion

The two clinical studies provided convincing evidence that Meningococcal A Conjugate Vaccine 5 µg is well tolerated and safe. Meningococcal A Conjugate Vaccine 5 µg would provide a substantial benefit given its demonstrated ability to elicit sustained functional immune responses in infants from the age of 14 weeks that are non- inferior to the immune responses induced by MenAfriVac (10 µg) which has proven highly effective. Clinical data allow its routine use within recommended EPI immunisations. The benefit-to-risk ratio of Meningococcal A

Conjugate Vaccine 5 µg appears to be highly favourable.

5.2 Pharmacokinetics properties
Evaluation of pharmacokinetics is not required for vaccines.

5.3 Pre clinical safety data
Meningococcal A Conjugate Vaccine has been shown to have no treatment-related effects in rats and mice following single and repeated (once a week for four weeks) intramuscular administrations at doses equivalent to up to three times the maximal dose intended for use in clinical studies.

In these species, the no-observed-effect-level (NOEL) of Meningococcal A Conjugate Vaccine was found to be greater than 30 µg/animal (i.e. greater than three times the intended human dose).

The local tolerance study carried out in the rabbit and using the intramuscular administration, which is the route, proposed for humans, showed local minor and reversible reactions generally described with adjuvanted/conjugated vaccines.
Preclinical data reveal no special hazard for humans based on general safety tests performed in animals.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients

Excipients of Meningococcal A Conjugate Vaccine 5 µg	Each single dose of 0.5mL contains
Mannitol	2.85 mg
Sucrose	0.72 mg
Tris(hydroxymethyl)aminomethane	0.06 mg

Components of Diluent for Meningococcal A Conjugate Vaccine 5 micrograms	Each mL contains
Al^{3+} as AlPO4 (adjuvant)	0.6 mg Al^{3+} 2.712 mg AlPO4
Thiomersal (preservative)	0.01%
Sodium chloride	0.90%
Water for Injection	q.s.

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

6.3 Shelf life
Shelf life of Meningococcal A Conjugate Vaccine: 3 years (36 months) Shelf life of Diluent for Meningococcal A Conjugate

Vaccine: 54 months
The expiry date of the vaccine and diluent is indicated on the label and packaging.
Once the vaccine has been reconstituted, it should be used the same day [preferably immediately but by no means beyond six (6) hours after reconstitution], and only then if the vial has been maintained between 2-8°C and protected from sunlight. Any opened container remaining at the end of a session should be discarded.

6.4 Special precautions for storage

Meningococcal Conjugate Vaccine 5 µg should be stored and transported between 2-8ºC. Protect from light. The diluent should be stored at below +40ºC, Do not freeze. It is recommended to protect the reconstituted vaccine from direct sunlight. Do not exceed the expiry date stated on the external packaging.

6.5 Nature and contents of container

Meningococcal A Conjugate Vaccine 5 µg is filled in 5.0 mL glass vials (USP Type I), stopped with bromobutyl rubber closures, type slotted and closed with flip off aluminium plastic caps (white flip off with copper gold body). The diluent is presented in a 5 mL glass ampoule.

6.6 Instructions for disposal and handling

Meningococcal A Conjugate Vaccine 5 µg is presented as a white vaccine pellet in a vial, with sterile diluents in a separate container.
The diluents and reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of physical aspects prior to administration. In the event of either being observed, the diluents or reconstituted vaccine should be discarded.
The vaccine must be reconstituted by adding the entire content of the supplied container of diluents (5.0 mL to 10 dose vial) to the vial containing the pellet, using a sterile syringe and sterile needle. Only the diluent provided must be used for reconstitution. After the addition of the diluents to the pellet, the mixture should be well shaken until the pellet is completely dissolved in the diluents.
A new sterile syringe and sterile needle should be used to administer each dose of the vaccine.

After reconstitution, the vaccine should be injected promptly. The reconstituted vaccine is a clear colorless solution.

7. MARKET AUTHORIZATION HOLDER

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