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TITLE

Neisseria meningitidis serogroups A, C, W_{135} and Y vaccine

SCOPE

Trade Names

MENCEVAX™ ACWY

MENCEVAX™ ACWY MONODOSE

Formulation and Strength

Mencevax ACWY is a lyophilised preparation of purified polysaccharides from *Neisseria meningitidis* (meningococcus) of serogroups A, C, W_{135} and Y.

Mencevax ACWY meets the World Health Organisation requirements for biological substances and for meningococcal meningitis vaccines.

Each 0.5 ml dose of reconstituted vaccine contains 50 μg of each of the polysaccharides of serogroups A, C, W_{135} and Y.

Powder and diluent for solution for injection.

Excipients

Powder: sucrose, trometamol

Diluent: sodium chloride, water for injections (+ phenol for multidose presentations).

CLINICAL INFORMATION

Indications

For the active immunization of adults and children over 2 years against meningococcal meningitis caused by meningococci of serogroups A, C, W_{135} and Y meningococci.

The vaccine is particularly recommended for subjects at risk, for example those living in or visiting areas where the disease is epidemic or highly endemic.

It is also recommended for subjects living in closed communities and close contacts of patients with disease caused by meningococci of serogroups A, C, W_{135} and Y.

Dosage and Administration

Posology

The recommended dose of the vaccine contained in 0.5 ml must be administered.

Individuals remaining at high risk of exposure to serogroups A, W_{135} and Y should be considered for re-vaccination two years after receipt of Mencevax ACWY according to local recommendations. These include:

- Residents in endemic area, staying longer than two years exposed to *Neisseria meningitidis* and previously vaccinated with Mencevax.
- Travellers leaving for a short period journey and previously vaccinated with Mencevax longer than 2 years ago.

Conjugate vaccines are recommended when re-vaccination within 2 years after administration of the previous Mencevax ACWY dose is considered.

(*see persistence of immune response in section "Clinical studies"*).

Method of administration

Mencevax ACWY is for **subcutaneous use** only.

For instructions on reconstitution of the medicinal product before administration (*see section "Use and Handling"*).

Contraindications

Hypersensitivity to the active substances or to any of the excipients (*see sections "Formulation and Strength" and "Excipients"*).

Hypersensitivity reaction after previous administration of Mencevax ACWY.

Warnings and Precautions

As with all injectable vaccines, appropriate medical treatment should always be readily available for treatment in case of anaphylactic reactions following the administration of the vaccine.

For this reason, the vaccinee should remain under medical supervision for 30 minutes after immunisation.

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

Vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

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

Mencevax ACWY will only confer protection against *Neisseria meningitidis* serogroups A, C, W_{135} and Y. As for any vaccine, complete protection cannot be guaranteed in every vaccinated individual. If administered to subjects with impaired immune responses, the vaccine may not induce an effective response.

Re-vaccination with serogroup C polysaccharide containing vaccines may induce lower antibody responses to meningococcal serogroup C polysaccharide compared to primary vaccination.

In subjects remaining at high risk of exposure to meningococcal disease caused by serogroups A, C, W_{135} and Y, re-vaccination should be considered according to official recommendations (*see section "Clinical studies"*).

Mencevax ACWY should under no circumstances be administered intravascularly.

Interactions

Mencevax ACWY can be administered at the same time as other vaccines.

The other injectable vaccines should always be administered at a different injection site.

Pregnancy and Lactation

Pregnancy

Adequate human data on use during pregnancy and adequate animal reproduction studies are not available.

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

Lactation

Adequate data on the administration of Mencevax ACWY to women who are breast-feeding are not available. However, as with other polysaccharide vaccines, one does not expect vaccination with Mencevax ACWY to harm the mother or the infant. Mencevax ACWY should be administered to women who are breast-feeding when needed and the possible advantages outweigh the possible risks.

Ability to Perform Tasks that Require Judgement, Motor or Cognitive Skills

There have been no studies to investigate the effect of Mencevax ACWY on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance. Nevertheless, the clinical status of the patient and the adverse event profile of Mencevax ACWY should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills.

Adverse Reactions

Clinical trial data

The safety profile presented below is based on data from clinical studies in which 530 subjects received Mencevax ACWY.

Adverse reactions occurring during these studies were mostly reported within 48 hours following vaccination.

Frequencies are reported as:

Very common: ≥ 1/10

Common: ≥ 1/100 to < 1/10

Uncommon: ≥ 1/1000 to < 1/100

Metabolism and nutrition disorders:

Common: appetite lost

Psychiatric disorders:

Very common: irritability

Nervous system disorders:

Very common: drowsiness, headache

Uncommon: dizziness

Gastrointestinal disorders:

Common: gastrointestinal symptoms e.g. nausea, vomiting and diarrhoea

Musculoskeletal and connective tissue disorders:

Common: myalgia

General disorders and administration site conditions:

Very common: pain and redness at the injection site, fatigue

Common: swelling at the injection site, fever

Post-marketing data

In addition, the following adverse reactions have been reported during post-marketing surveillance:

Immune system disorders

Allergic reactions, including anaphylactic and anaphylactoid reactions

Skin and subcutaneous tissue disorders

Urticaria, rash, angioneurotic oedema

Musculoskeletal and connective tissue disorders

Arthralgia, musculoskeletal stiffness

General disorders and administration site conditions

Influenza-like symptoms, chills

Overdosage

Cases of overdose (up to 10 times the recommended dose) have been reported during post-marketing surveillance. Adverse events reported following overdosage were similar to those reported with normal vaccine administration.

Clinical Pharmacology

Pharmacodynamics

ATC Code

Pharmacotherapeutic group: Bacterial vaccines ATC code: J07AH04

Mechanism of Action

Mencevax ACWY induces bactericidal antibodies against meningococci of the serogroups A, C, W_{135} and Y.

Pharmacodynamic Effects

See section "*Clinical studies*".

Pharmacokinetics

Evaluation of pharmacokinetic properties is not required for vaccines.

Clinical Studies

Immunogenicity data

Mencevax ACWY induces bactericidal antibodies against meningococci of the serogroups A, C, W_{135} and Y.

Clinical studies have evaluated one month after vaccination with Mencevax ACWY (N=530) the percentage of subjects with bactericidal antibody titres ≥ 1:8, the vaccine response (defined as seroconversion with SBA titre cut-off of 1:8 for initially seronegative subjects or defined as four-fold increase in SBA titres from pre- to post-vaccination for initially seropositive subjects) and the seroconversion rate in subjects who were seronegative prior to vaccination.

The results obtained in those clinical studies for all serogroups are summarised in the table below:

	Serogroup							
	MenA		MenC		$MenW_{135}$		MenY	
	N	%	N	%	N	%	N	%
rSBA* ≥ 1:8								
2-5 years of age	169	99.4	169	85.8	149	96.6	175	100
≥ 6 years of age	310	100	315	99.7	316	99.7	316	100
Vaccine response								
2-5 years of age	141	72.3	160	80.6	146	89.7	165	73.9
≥ 6 years of age	295	78.6	309	96.4	306	92.5	304	84.2
Seroconversion in S-								
2-5 years of age	13	92.3	132	81.8	88	94.3	40	100
≥ 6 years of age	3	100	180	99.4	125	100	46	100

N=number of subjects

*rSBA testing performed at GSK

The seroconversion rate of children vaccinated under the age of two years is lower for the serogroups C, W_{135} and Y. However, based on literature data, the seroconversion rate for the serogroup A appears to be acceptable in children from the age of 6 months onwards.

Studies conducted among late complement component deficient subjects (LCCD) (N=31) and subjects after Bone Marrow Transplant (BMT) (N=44) demonstrated that vaccination with Mencevax ACWY elicited a satisfactory immune response. In LCCD patients, GMCs of 26.8 μg/ml for MenA, 19.2 μg/ml for MenC, 16.4 μg/ml for $MenW_{135}$ and 30.7 μg/ml for MenY were observed at 13 weeks after vaccination. In BMT patients, 62% to 84% of subjects had anti-PSA concentrations ≥ 2.0 μg/ml and 76% to 84% of subjects had anti-PSC concentrations ≥ 2.0 μg/ml one month after vaccination.

Efficacy data

In response to a meningococcal disease epidemic in Burkina Faso, a mass vaccination campaign with Mencevax ACW was performed in more than 1.68 million children and adults aged from 2 to 29 years. Following this mass vaccination campaign 32 cases of meningitis due to *Neisseria meningitidis* serogroup A and 3 cases of meningitis due to *Neisseria meningitidis* serogroup W_{135} were reported.

Persistence of immune response

The persistence of the immune response elicited by Mencevax ACWY was evaluated up to 5 years after vaccination in adolescents and adults aged 11-55 years primed in study MenACWY-TT-015 conducted in the Philippines and Saudi Arabia (Table 1). The rSBA data generated at Public Health England (PHE) laboratories, indicate that among individuals 11-55 years of age who were vaccinated two years earlier with Mencevax ACWY, immunity to groups W_{135} and Y persists in 24.0% and 44.0%, respectively.

The persistence of the immune response elicited by Mencevax ACWY was evaluated 12 months after vaccination in children aged 2-10 years in study MenACWY-TT-027 conducted in Finland (Table 2) and up to 15 months after vaccination in children aged 3-5 years in study MenACWY-TT-013 conducted in Austria and Germany (Table 3). Limited data from these two clinical studies showed a waning of serum bactericidal antibody titres one year post-vaccination when using human complement in the assay (hSBA).

The clinical relevance of the waning of antibody titres is unknown and data suggest that re-vaccination may be appropriate for individuals who remain at high risk of exposure to *Neisseria meningitidis*. Use of conjugate vaccines is recommended when re-vaccination within two years after administration of the previous Mencevax ACWY dose. The risk of hyporesponsiveness precludes the use of non-conjugated polysaccharide vaccines within this time period.

Table 1: 5-year persistence data (rSBA) in adolescents and adults aged 11-55 years at vaccination

Group		Time-point	N*	rSBA** ≥ 1:8 (95%CI)	GMT (95%CI)
A	Mencevax ACWY	Month 1	19	100% (82.4; 100)	1463.2 (886.5; 2415.0)
		Year 1	19	84.2% (60.4; 96.6)	218.0 (71.0; 669.6)
		Year 2	98	91.8% (84.5; 96.4)	385.8 (259.4; 573.9)
		Year 4	107	73.8% (64.4; 81.9)	105.4 (67.6; 164.4)
		Year 5	105	74.3% (64.8; 82.3)	103.6 (67.8; 158.3)
	MenACWY-TT	Month 1	30	100% (88.4; 100)	4231.2 (2730.0; 6556.2)
		Year 1	30	93.3% (77.9; 99.2)	1066.9 (472.4; 2409.6)
		Year 2	99	94.9% (88.6; 98.3)	807.1 (559.5; 1164.2)
		Year 4	312	86.5% (82.2; 90.1)	278.6 (219.7; 353.2)
		Year 5	299	90.0% (86.0; 93.1)	303.9 (248.2; 372.0)

Group		Time-point	N*	rSBA** ≥ 1:8 (95%CI)	GMT (95%CI)
C	Mencevax ACWY	Month 1	18	100% (81.5; 100)	8070.7 (4896.6; 13302.2)
		Year 1	17	94.1% (71.3; 99.9)	1956.8 (731.8; 5232.7)
		Year 2	99	86.9% (78.6; 92.8)	286.3 (181.8; 450.9)
		Year 4	107	84.1% (75.8; 90.5)	315.0 (196.8; 504.1)
		Year 5	104	71.2% (61.4; 79.6)	142.4 (85.3; 237.6)
	MenACWY-TT	Month 1	30	100% (88.4; 100)	6886.0 (4473.9; 10598.7)
		Year 1	30	96.7% (82.8; 99.9)	462.7 (239.2; 895.2)
		Year 2	100	98.0% (93.0; 99.8)	304.4 (232.0; 399.5)
		Year 4	312	88.5% (84.4; 91.8)	273.6 (220.6; 339.4)
		Year 5	299	79.3% (74.2; 83.7)	114.0 (90.5; 143.5)
W_{135}	Mencevax ACWY	Month 1	17	76.5% (50.1; 93.2)	881.6 (150.8; 5154.0)
		Year 1	18	66.7% (41.0; 86.7)	120.3 (23.6; 614.5)
		Year 2	100	24% (16.0; 33.6)	6.5 (4.2; 10.0)
		Year 4	107	25.2% (17.3; 34.6)	11.3 (7.8; 16.3)
		Year 5	105	24.8% (16.9; 34.1)	11.7 (7.9; 17.1)
	MenACWY-TT	Month 1	30	96.7% (82.8; 99.9)	9571.6 (4649.0; 19706.4)
		Year 1	30	93.3% (77.9; 99.2)	1659.2 (728.5; 3778.7)
		Year 2	100	84.0% (75.3; 90.6)	257.8 (161.8; 410.7)
		Year 4	312	74.0% (68.8; 78.8)	175.1 (131.5; 233.0)
		Year 5	299	71.6% (66.1; 76.6)	170.2 (124.7; 232.4)
Y	Mencevax ACWY	Month 1	12	100% (73.5; 100)	2663.0 (1821.9; 3892.4)
		Year 1	12	50.0% (21.1; 78.9)	22.3 (3.4; 146.2)
		Year 2	100	44.0% (34.1; 54.3)	19.4 (11.4; 33.0)
		Year 4	107	43.9% (34.3; 53.9)	26.0 (16.6; 40.7)
		Year 5	105	44.8% (35.0; 54.8)	29.6 (18.7; 46.7)
	MenACWY-TT	Month 1	27	100% (87.2; 100)	3659.5 (2193.4; 6105.6)
		Year 1	28	96.4% (81.7; 99.9)	1157.7 (572.2; 2342.3)
		Year 2	100	86.0% (77.6; 92.1)	367.1 (232.2; 580.2)
		Year 4	309	82.8% (78.2; 86.9)	350.5 (268.9; 456.7)
		Year 5	299	84.3% (79.7; 88.2)	306.0 (236.3; 396.3)

GMT: Geometric Mean Titre

MenACWY-TT: Meningococcal group A, C, W_{135} and Y vaccine conjugated to tetanus toxoid

* For one Month 1, Year 1 and Year 2 post-vaccination time points, a subset of samples were tested with PHE rSBA assays

**rSBA testing performed at PHE laboratories in UK

Table 2: 1-year persistence data (hSBA) in children aged 2 to 10 years at vaccination

Group	Response to	Time-point	hSBA*		
			N	≥ 4 (95%CI)	GMT (95%CI)
A	Mencevax ACWY	Month 1	35	25.7% (12.5; 43.3)	4.1 (2.6; 6.5)
		Year 1	35	11.4% (3.2; 26.7)	2.5 (1.9; 3.3)
	MenACWY-TT	Month 1	111	82.0% (73.6; 88.6)	57.0 (40.3; 80.6)
		Year 1	104	18.3% (11.4; 27.1)	3.5 (2.7; 4.4)
C	Mencevax ACWY	Month 1	38	39.5% (24.0; 56.6)	13.1 (5.4; 32.0)
		Year 1	31	32.3% (16.7; 51.4)	7.7 (3.5; 17.3)
	MenACWY-TT	Month 1	107	89.7% (82.3; 94.8)	154.8 (101.1; 237.1)
		Year 1	105	95.2% (89.2; 98.4)	129.5 (95.4; 175.9)
W_{135}	Mencevax ACWY	Month 1	35	34.3% (19.1; 52.2)	5.8 (3.3; 9.9)
		Year 1	31	12.9% (3.6; 29.8)	3.4 (2.0; 5.8)
	MenACWY-TT	Month 1	107	95.3% (89.4; 98.5)	134.2 (101.4; 177.6)
		Year 1	103	100% (96.5; 100)	256.7 (218.2; 301.9)
Y	Mencevax ACWY	Month 1	32	43.8% (26.4; 62.3)	12.5 (5.6; 27.7)
		Year 1	36	33.3% (18.6; 51.0)	9.3 (4.3; 19.9)
	MenACWY-TT	Month 1	94	84.0% (75.0; 90.8)	93.7 (62.1; 141.4)
		Year 1	106	99.1% (94.9; 100)	265.0 (213.0; 329.6)

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

GMT: Geometric Mean Titre

MenACWY-TT: Meningococcal group A, C, W_{135} and Y vaccine conjugated to tetanus toxoid

* hSBA testing performed at GSK laboratories

Table 3: 15-month persistence data (hSBA) in children aged 3 to 5 years at vaccination

Group	Response to	Time-point	hSBA*		
			N	≥ 4 (95%CI)	GMT (95%CI)
A	Mencevax ACWY	Month 1	26	42.3% (23.4; 63.1)	5.9 (3.2; 11.0)
		Month 15	14	7.1% (0.2; 33.9)	2.2 (1.8; 2.7)
	MenACWY-TT	Month 1	42	83.3% (68.6; 93.0)	23.7 (14.8; 38.1)
		Month 15	24	20.8% (7.1; 42.2)	3.5 (2.2; 5.7)
C	Mencevax ACWY	Month 1	14	92.9% (66.1; 99.8)	25.7 (12.6; 52.7)
		Month 15	22	77.3% (54.6; 92.2)	28.1 (12.9; 61.0)
	MenACWY-TT	Month 1	23	95.7% (78.1; 99.9)	95.0 (53.6; 168.5)
		Month 15	35	94.3% (80.8; 99.3)	112.4 (70.2; 180.0)
W_{135}	Mencevax ACWY	Month 1	22	63.6% (40.7; 82.8)	49.6 (14.9; 165.4)
		Month 15	6	33.3% (4.3; 77.7)	8.1 (0.8; 79.7)
	MenACWY-TT	Month 1	40	90.0% (76.3; 97.2)	284.0 (154.5; 522.0)
		Month 15	24	95.8% (78.9; 99.9)	221.5 (136.8; 358.7)
Y	Mencevax ACWY	Month 1	28	53.6% (33.9; 72.5)	10.8 (5.3; 21.9)
		Month 15	19	63.2% (38.4; 83.7)	20.9 (7.4; 58.9)
	MenACWY-TT	Month 1	38	92.1% (78.6; 98.3)	55.7 (35.9; 86.5)
		Month 15	32	90.6% (75.0; 98.0)	92.3 (48.6; 175.1)

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

GMT: Geometric Mean Titre

MenACWY-TT: Meningococcal group A, C, W_{135} and Y vaccine conjugated to tetanus toxoid

*hSBA testing performed at GSK laboratories

NON-CLINICAL INFORMATION

Animal Toxicology and/or Pharmacology

Non-clinical data reveal no special hazard for humans based on general safety tests performed in animals.

PHARMACEUTICAL INFORMATION

Shelf-life

The expiry date of the vaccine is indicated on the label and packaging.

After reconstitution, the vaccine should be injected promptly or kept in a refrigerator. If it is not used within eight hours, it should be discarded because of the risk of contamination.

It is recommended to protect the reconstituted vaccine from direct sunlight.

Storage

Store in a refrigerator (2°C – 8°C).

The diluent may also be stored at ambient temperature (25°C).

When supplies of Mencevax ACWY are distributed from a central cold-store, it is good practice to arrange transport under refrigerated conditions, particularly in hot climates.

Nature and Contents of Container

Mencevax ACWY is presented as a white powder in a glass vial.

The sterile diluent for the monodose presentation is clear and colourless and presented in a glass vial, pre-filled syringe or ampoule.

The sterile diluent for the multidose presentation (which contains phenol) can show a slight cloudiness and/or pink coloration and is presented in a glass vial.

Incompatibilities

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

Use and Handling

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

Mencevax ACWY must be reconstituted by adding the entire contents of the supplied container of diluent to the vial containing the powder. The powder should be completely dissolved in the diluent.

NAME OF MANUFACTURER

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