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PANDEMRIX™

1. NAME OF THE MEDICINAL PRODUCT

Pandemrix™ suspension and emulsion for emulsion for injection.
Influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After mixing, 1 dose (0.5 ml) contains:

Split influenza virus, inactivated, containing antigen* equivalent to:

A/California/07/2009 (H1N1) derived strain used NYMC X-179A 3.75 micrograms**

* propagated in eggs

** haemagglutinin

AS03 adjuvant composed of squalene (10.69 milligrams), DL- α -tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams)

The suspension and emulsion, once mixed, form a multidose vaccine in a vial. See section 6.5 for the number of doses per vial.

Excipient with known effect:

The vaccine contains 5 micrograms thiomersal

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension and emulsion for emulsion for injection.
The suspension is a colourless light opalescent liquid.
The emulsion is a whitish homogeneous liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of influenza in an officially declared pandemic situation.

Pandemrix should be used in accordance with Official Guidance.

4.2 Posology and method of administration

Posology

The dose recommendations take into account the safety and immunogenicity data from clinical studies in healthy subjects
See sections 4.4, 4.8 and 5.1 for details.

No data are available in children aged less than 6 months.

Adults aged 18 years and older:

One dose of 0.5 ml at an elected date.

Immunogenicity data obtained at three weeks after one dose of Pandemrix (H1N1)v suggest that a single dose may be sufficient.

If a second dose is administered there should be an interval of at least three weeks between the first and the second dose.

See section 5.1 regarding immune responses to one and two doses of Pandemrix (H1N1)v, including antibody levels after 6 and 12 months.

Paediatric population

Children and adolescents aged 10-17 years

Dosing may be in accordance with the recommendations for adults.

Children aged from 6 months to 9 years

One dose of 0.25 ml at an elected date.

There is a further immune response to a second dose of 0.25 ml administered after an interval of three weeks.

The use of a second dose should take into consideration the information provided in sections 4.4, 4.8 and 5.1.

Children aged less than 6 months

No data are available.

It is recommended that subjects who receive a first dose of Pandemrix should complete the vaccination course with Pandemrix (see section 4.4).

Method of administration

Immunisation should be carried out by intramuscular injection preferably into the deltoid muscle or anterolateral thigh (depending on the muscle mass).

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

4.3 Contraindications

History of an anaphylactic (i.e. life-threatening) reaction to any of the constituents or trace residues (egg and chicken protein, ovalbumin, formaldehyde, gentamicin sulphate and sodium deoxycholate) of this vaccine.

Immunisation should be postponed in subjects with a severe febrile illness or acute infection.

4.4 Special warnings and precautions for use

The vaccine can only be expected to protect against influenza caused by A/California/07/2009 (H1N1)v-like strains.

Caution is needed when administering this vaccine to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance, to any of the excipients listed in section 6.1, to thiomersal and to residues (egg and chicken protein, ovalbumin, formaldehyde, gentamicin sulphate and sodium deoxycholate).

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.

Pandemrix should under no circumstances be administered intravascularly.

There are no data with Pandemrix using the subcutaneous route. Therefore, healthcare providers need to assess the benefits and potential risks of administering the vaccine in individuals with thrombocytopenia or any bleeding disorder that would contraindicate intramuscular injection unless the potential benefit outweighs the risk of bleedings.

Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.

A protective immune response may not be elicited in all vaccinees (see section 5.1).

There are no safety, immunogenicity or efficacy data to support interchangeability of Pandemrix with other (H1N1)v vaccines.

Epidemiological studies relating to Pandemrix in several European countries have indicated an increased risk of narcolepsy with or without cataplexy in vaccinated as compared with unvaccinated individuals. In children/adolescents (aged up to 20 years), these studies have indicated an additional 1.4 to 8 cases in 100,000 vaccinated subjects. Available epidemiological data in adults aged over 20 years have indicated approximately 1 additional case per 100,000 vaccinated subjects. These data suggest that the excessive risk tends to decline with increasing age at vaccination.

The relationship between Pandemrix and narcolepsy is still under investigation.

Pandemrix should only be used if the recommended annual seasonal trivalent/quadrivalent influenza vaccines are not available and if immunisation against (H1N1)v is considered necessary (see section 4.8).

Paediatric population

There are no safety and immunogenicity data available from clinical studies with Pandemrix (H1N1)v in children aged less than 6 months. Vaccination is not recommended in this age group.

In children aged 6 to 35 months (N=51) who received two doses of 0.25 ml (half of the adult dose) with an interval of 3 weeks between doses there was an increase in the rates of injection site reactions and general symptoms after the second dose (see section 4.8). In particular rates of fever (axillary temperature $\geq 38^{\circ}\text{C}$) increased considerably after the second dose. Therefore, monitoring of temperature and measures to lower the fever (such as antipyretic medication as seems clinically necessary) are recommended in young children (e.g. up to approximately 6 years of age) after each dose of Pandemrix.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Data obtained on co-administration of Pandemrix (H1N1)v with non-adjuvanted seasonal influenza vaccine (Fluarix, a split virion vaccine) in healthy adults aged over 60 years did not suggest any significant interference in the immune response to Pandemrix (H1N1)v. The immune response to Fluarix was satisfactory.

Co-administration was not associated with higher rates of local or systemic reactions compared to administration of Pandemrix alone.

Therefore the data indicate that Pandemrix may be co-administered with non-adjuvanted seasonal influenza vaccines (with injections made into opposite limbs).

Data obtained on the administration of a non-adjuvanted seasonal influenza vaccine (Fluarix, as above) three weeks before a dose of Pandemrix (H1N1)v in healthy adults over 60 years of age, did not suggest any significant interference in the immune response to Pandemrix (H1N1)v. Therefore the data indicate that Pandemrix may be administered three weeks after the administration of non-adjuvanted seasonal influenza vaccines.

In a clinical study where a non-adjuvanted seasonal influenza vaccine (Fluarix, as above) was administered 3 weeks after the second dose of Pandemrix (two doses were given 21 days apart), a lower immune response to Fluarix was observed as compared to subjects who had not previously received Pandemrix. It is not known whether the observed effects would apply to administration of non-adjuvanted seasonal influenza vaccine after a single dose of Pandemrix or when longer dose intervals have elapsed since administration of Pandemrix. It is preferable that non-adjuvanted seasonal influenza vaccines should be administered before or with the first dose of Pandemrix.

There are no data on co-administration of Pandemrix with other vaccines.

If co-administration with another vaccine is considered, immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

The immunological response may be diminished if the patient is undergoing immunosuppressant treatment.

Following influenza vaccination, false-positive serology test results may be obtained by the ELISA method for antibody to human immunodeficiency virus-1 (HIV-1), hepatitis C virus and, especially, HTLV-1. In such cases, the Western blot method is negative. These transitory false-positive results may be due to IgM production in response to the vaccine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pandemrix has been administered to women in each trimester of pregnancy. Information on outcomes from estimated more than 200,000 women who have been vaccinated during pregnancy is currently limited. There was no evidence of an increased risk of adverse outcomes in over 100 pregnancies that were followed in a prospective clinical study.

Animal studies with Pandemrix do not indicate reproductive toxicity (see section 5.3).

Data from pregnant women vaccinated with different inactivated non-adjuvanted seasonal vaccines do not suggest malformations or fetal or neonatal toxicity.

Breast-feeding

Pandemrix may be administered in lactating women.

Fertility

No fertility data are available.

4.7 Effects on ability to drive and use machines

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

Clinical studies have evaluated the incidence of adverse reactions in more than 1,000 subjects 18 years old and above who received Pandemrix (H1N1).

In adults 18 to 60 years of age, the most frequently reported adverse reactions after vaccination were injection site pain (87.8%), fatigue (32.9%), headache (28.1%), arthralgia (17.9%), myalgia (30.0%), shivering (19.4%), injection site swelling (11.5%) and sweating (11.3%).

In subjects > 60 years of age, the most frequently reported adverse reactions after vaccination were injection site pain (59.0%), myalgia (20.6%), fatigue (17.9%), headache (17.6%) and arthralgia (14.3%).

Tabulated list of adverse reactions

Adverse reactions reported are listed per dose according to the following frequency:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Frequency	Adverse reactions
Clinical trials		
Blood and lymphatic system disorders	Uncommon	Lymphadenopathy
Psychiatric disorders	Uncommon	Insomnia
Nervous system disorders	Very common	Headache
	Uncommon	Paraesthesia, dizziness
Gastrointestinal disorders	Common	Gastrointestinal symptoms (such as diarrhoea, vomiting, abdominal pain, nausea)
Skin and subcutaneous tissue disorders	Very common	Sweating increased
	Uncommon	Pruritus, rash
Musculoskeletal and connective tissue disorders	Very common	Arthralgia, myalgia

General disorders and administration site conditions	Very common	Swelling and pain at the injection site, fatigue, shivering
	Common	Redness and pruritus at the injection site, fever
	Uncommon	induration and warmth at the injection site, influenza like illness, malaise
Post-marketing experience with Pandemrix (H1N1)v		
Immune system disorders		Anaphylaxis, allergic reactions
Nervous system disorders	Very rare ¹	Febrile convulsions
		Narcolepsy with or without cataplexy (see section 4.4)
		Somnolence ²
Skin and subcutaneous tissue disorders		Angioedema, generalised skin reactions, urticaria
General disorders and administration site conditions		Injection site reactions (such as inflammation, mass, ecchymosis)
Post-marketing experience with trivalent seasonal influenza vaccines		
Blood and lymphatic system disorders	Rare	Transient thrombocytopenia
Nervous system disorders	Rare	Neuralgia
	Very rare	Neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome
Vascular disorders	Very rare	Vasculitis with transient renal involvement

¹frequency based on estimated attributable risk from epidemiological studies in several European countries (see section 4.4)

²Reported in patients with narcolepsy and as a temporary event following vaccination.

In clinical studies that evaluated reactogenicity in adults aged 18 years and above who received two 0.5 ml doses of Pandemrix (H1N1)v, higher rates of general solicited symptoms (such as fatigue, headache, arthralgia, myalgia, shivering, sweating and fever) were observed after the second dose compared to the first dose.

Paediatric population

Children aged 10-17 years

In clinical studies that evaluated the reactogenicity in children 10 to 17 years of age who received either two 0.5 ml doses (adult dose) or two 0.25 ml doses (half adult dose) (21 days apart) of Pandemrix (H1N1)v, the per-dose frequency of the following adverse reactions was as shown in the table:

Adverse reactions	10-17 years			
	Half adult dose		Adult dose	
	Post dose 1 N=118	Post dose 2 N=117	Post dose 1 N=98	Post dose 2 N=93
Pain	73.7%	68.4%	92.9%	96.8%
Redness	22.9%	31.6%	21.4%	28.0%
Swelling	30.5%	25.6%	41.8%	53.8%
Shivering	20.3%	16.2%	14.3%	26.9%
Sweating	7.6%	6.8%	5.1%	7.5%
Fever >38°C	1.7%	5.1%	3.1%	9.7%

Fever >39°C	1.7%	1.7%	0.0%	1.1%
Arthralgia	9.3%	15.4%	26.5%	34.4%
Myalgia	22.0%	23.1%	34.7%	47.3%
Fatigue	28.0%	27.4%	40.8%	51.6%
Gastrointestinal	11.0%	12.0%	6.1%	6.5%
Headache	35.6%	35.0%	41.8%	53.8%

Children aged 3-9 years

In clinical studies that evaluated reactogenicity in children 3 to 5 and 6 to 9 years of age who received either two 0.25 ml doses (half adult dose) or two 0.5 ml doses (adult dose) (21 days apart) of Pandemrix (H1N1)v, the per-dose frequency of the following adverse reactions was as shown in the table:

Adverse reactions	3-5 years				6-9 years			
	Half adult dose		Adult dose		Half adult dose		Adult dose	
	Post dose 1 N=60	Post dose 2 N=56	Post dose 1 N=53	Post dose 2 N=52	Post dose 1 N=65	Post dose 2 N=63	Post dose 1 N=57	Post dose 2 N=57
Pain	60.0%	55.4%	75.5%	84.6%	63.1%	65.1%	94.7%	96.5%
Redness	26.7%	41.1%	28.3%	34.6%	23.1%	33.3%	24.6%	33.3%
Swelling	21.7%	28.6%	34.0%	30.8%	23.1%	25.4%	28.1%	45.6%
Shivering	13.3%	7.1%	3.8%	9.6%	10.8%	6.3%	7.0%	22.8%
Sweating	10.0%	5.4%	1.9%	7.7%	6.2%	7.9%	1.8%	7.0%
Fever >38°C	10.0%	14.3%	5.7%	32.6%	4.6%	6.4%	1.8%	12.3%
Fever >39°C	1.7%	5.4%	0.0%	3.8%	0.0%	3.2%	0.0%	1.8%
Diarrhoea	5.0%	5.4%	1.9%	5.8%	NA	NA	NA	NA
Drowsiness	23.3%	17.9%	15.1%	28.8%	NA	NA	NA	NA
Irritability	20.0%	26.8%	18.9%	26.9%	NA	NA	NA	NA
Loss of appetite	20.0%	17.9%	15.1%	32.7%	NA	NA	NA	NA
Arthralgia	NA	NA	NA	NA	15.4%	14.3%	14.0%	22.8%
Myalgia	NA	NA	NA	NA	16.9%	17.5%	22.8%	28.1%
Fatigue	NA	NA	NA	NA	27.7%	20.6%	35.1%	49.1%
Gastrointestinal	NA	NA	NA	NA	13.8%	7.9%	15.8%	14.0%
Headache	NA	NA	NA	NA	21.5%	20.6%	42.1%	45.6%

NA= not available

Children aged 6-35 months

In a clinical study that evaluated reactogenicity in children aged 6 to 35 months who received either two 0.25 ml doses (half adult dose) or two 0.5 ml doses (adult dose) (21 days apart) of Pandemrix (H1N1)v there was an increase in injection site reactions and general symptoms after the second dose compared to the first dose particularly in rates of axillary fever (>38°C). The per-dose frequency of the following adverse reactions was as shown in the table:

Adverse reactions	Half adult dose		Adult dose	
	Post dose 1 N=104	Post dose 2 N=104	Post dose 1 N=53	Post dose 2 N=52
Pain	35.6%	41.3%	58.5%	51.9%
Redness	18.3%	32.7%	32.1%	44.2%
Swelling	11.5%	28.8%	20.8%	32.7%
Fever (>38°C) axillary	6.8%	41.4%	7.6%	46.1%

Fever (>39°C) axillary	1.0%	2.9%	1.9%	17.3%
Drowsiness	16.3%	33.7%	20.8%	42.3%
Irritability	26.9%	43.3%	22.6%	51.9%
Loss of appetite	17.3%	39.4%	20.8%	50.0%

This medicinal product contains thiomersal (an organomercuric compound) as a preservative and therefore, it is possible that sensitisation reactions may occur (see section 4.4).

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 to the Ministry of Health according to the National Regulation by using an online form

(<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il>) or by email (adr@moh.health.gov.il). Additionally, you should also report to GSK Israel (il.safety@gsk.com).

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccines, ATC Code: J07BB02.

Pharmacodynamic effects

Immune response to Pandemrix (H1N1)v

Adults aged 18-60 years

Two clinical studies evaluated the immunogenicity of Pandemrix in healthy subjects aged 18-60 years. All subjects received two doses of 0.5 ml 21 days apart, except in study D-Pan H1N1-008, in which half of the subjects received only one dose of 0.5 ml. The anti-HA antibody responses were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like							
	D-Pan H1N1-007				D-Pan H1N1-008			
	21 days after 1 st dose		21 days after 2 nd dose		21 days after 1 st dose		21 days after 2 nd dose	
	Total enrolled subjects N=60 [95% CI]	Sero- negative subjects prior to vaccination N=37 [95% CI]	Total enrolled subjects N=59 [95% CI]	Sero- negative subjects prior to vaccination N=37 [95% CI]	Total enrolled subjects N=120 [95% CI]	Sero- negative subjects prior to vaccination N=76 [95% CI]	Total enrolled subjects N=66 [95% CI]	Sero- negative subjects prior to vaccination N=42 [95% CI]
Sero- protection rate ¹	100% [94.0; 100]	100% [90.5;100]	100% [93.9; 100]	100% [90.5;100]	97.5% [92.9; 99.5]	96.1% [88.9;99.2]	100% [94.6; 100]	100% [91.6;100]

Sero-conversion rate ²	98.3% [91.1; 100]	100% [90.5; 100]	98.3% [90.9; 100]	100% [90.5; 100]	95.0% [89.4; 98.1]	96.1% [88.9; 99.2]	98.5% [91.8; 100]	100% [91.6; 100]
Sero-conversion factor ³	38.1	47.0	72.9	113.3	42.15 [33.43; 53.16]	50.73 [37.84; 68.02]	69.7 [53.79; 90.32]	105.9 [81.81; 137.08]

¹ seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre $\geq 1:40$; ² seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of $\geq 1:40$, or who were seropositive at pre-vaccination and have a 4-fold increase in titre; ³ seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

Six months after the first dose, the seroprotection rate was as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like					
	D-Pan H1N1-007		D-Pan H1N1-008			
	Month 6 after 2 doses of 0.5 ml		Month 6 after 2 doses of 0.5 ml		Month 6 after 1 dose of 0.5 ml	
	Total enrolled subjects N=59 [95% CI]	Sero-negative subjects prior to vaccination N=35 [95% CI]	Total enrolled subjects N=67 [95% CI]	Sero-negative subjects prior to vaccination N=43 [95% CI]	Total enrolled subjects N=51 [95% CI]	Sero-negative subjects prior to vaccination N=32 [95% CI]
Seroprotection rate ¹	100% [93.9; 100]	100% [90.0; 100]	97.0% [89.6; 99.6]	95.3% [84.2; 99.4]	86.3% [73.7; 94.3]	78.1% [60.0; 90.7]

¹ seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre $\geq 1:40$

Twelve months after the first dose, the seroprotection rate was as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like					
	D-Pan H1N1-007		D-Pan H1N1-008			
	Month 12 after 2 doses of 0.5 ml		Month 12 after 2 doses of 0.5 ml		Month 12 after 1 dose of 0.5 ml	
	Total enrolled subjects N=59 [95% CI]	Sero-negative subjects prior to vaccination N=36 [95% CI]	Total enrolled subjects N=67 [95% CI]	Sero-negative subjects prior to vaccination N=43 [95% CI]	Total enrolled subjects N=52 [95% CI]	Sero-negative subjects prior to vaccination N=32 [95% CI]
Seroprotection rate ¹	78.0% [65.3; 87.7]	66.7% [49.8; 80.9]	79.1% [67.4; 88.1]	69.8% [53.9; 82.8]	65.4% [50.9; 78.0]	53.1% [34.7; 70.9]

¹ seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre $\geq 1:40$

In study D-Pan-H1N1-008, the neutralising antibody responses were as follows:

Serum neutralising antibody	Immune response to A/Netherlands/602/9 (H1N1)v-like ¹					
	After 2 doses of 0.5 ml			After 1 dose of 0.5 ml		
	Day 21	Day 42	Month 6	Day 21	Day 42	Month 6

	N=22	N=22	N=22	N=17	N=17	N=17
Vaccine Response Rate ²	68.2% [45.1;86.1]	90.9% [70.8;98.9]	81.8% [59.7;94.8]	70.6% [44.0;89.7]	64.7% [38.3;85.8]	35.3% [14.2;61.7]

¹antigenically similar to A/California/7/2009 (H1N1)v-like

²percentage of vaccinees who, if initially seronegative reach an antibody titre ≥ 32 1/DIL after vaccination or, if initially seropositive reach an antibody titre ≥ 4 fold the pre-vaccination antibody titre

Elderly (>60 years)

The anti-HA antibody responses in healthy subjects aged >60 years who received either one or two doses of 0.5 ml 21 days apart were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like							
	61-70 years				71-80 years			
	21 days after 1 st dose		21 days after 2 nd dose		21 days after 1 st dose		21 days after 2 nd dose	
	Total enrolled subjects N=75 [95% CI]	Sero-negative subjects prior to vaccination N=43 [95% CI]	Total enrolled subjects N=40 [95% CI]	Sero-negative subjects prior to vaccination N=23 [95% CI]	Total enrolled subjects N=40 [95% CI]	Sero-negative subjects prior to vaccination N=23 [95% CI]	Total enrolled subjects N=24 [95% CI]	Sero-negative subjects prior to vaccination N=15 [95% CI]
Sero-protection rate ¹	88.0% [78.4; 94.4]	81.4% [66.6;91.6]	97.5% [86.8; 99.9]	95.7% [78.1;99.9]	87.5% [73.2; 95.8]	82.6% [61.2;95.0]	100% [85.8; 100]	100% [78.2;100]
Sero-conversion rate ²	80.0% [69.2; 88.4]	81.4% [66.6;91.6]	95.0% [83.1; 99.4]	95.7% [78.1;99.9]	77.5% [61.5; 89.2]	82.6% [61.2;95.0]	91.7% [73.0; 99.0]	100% [78.2;100]
Sero-conversion factor ³	13.5 [10.3; 17.7]	20.3 [13.94; 28.78]	37.45 [25.29; 55.46]	62.06 [42.62; 90.37]	13.5 [8.6; 21.1]	20.67 [11.58; 36.88]	28.95 [17.02; 49.23]	50.82 [32.97; 78.35]

¹seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre $\geq 1:40$;

²seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of $\geq 1:40$, or who were seropositive at pre-vaccination and have a 4-fold increase in titre;

³seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like			
	>80 years			
	21 days after 1 st dose		21 days after 2 nd dose	
	Total enrolled subjects N=5 [95% CI]	Seronegative subjects prior to vaccination N=3 [95% CI]	Total enrolled subjects N=3 [95% CI]	Seronegative subjects prior to vaccination N=1 [95% CI]
Seroprotection rate ¹	80.0% [28.4;99.5]	66.7% [9.4;99.2]	100% [29.2;100]	100% [2.5;100]
Seroconversion rate ²	80.0% [28.4;99.5]	66.7% [9.4;99.2]	100% [29.2;100]	100% [2.5;100]
Seroconversion	18.4	17.95	25.49	64.0

factor ³	[4.3;78.1]	[0.55;582.25]	[0.99;654.60]	
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¹ seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre $\geq 1:40$;

² seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of $\geq 1:40$, or who were seropositive at pre-vaccination and have a 4-fold increase in titre;

³ seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

Six months after the first dose, the seroprotection rate was as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like							
	61-70 years				71-80 years			
	Month 6 after 2 doses of 0.5 ml		Month 6 after 1 dose of 0.5 ml		Month 6 after 2 doses of 0.5 ml		Month 6 after 1 dose of 0.5 ml	
	Total enrolled subjects N=41 [95% CI]	Sero-negative subjects prior to vaccination N=23 [95% CI]	Total enrolled subjects N=33 [95% CI]	Sero-negative subjects prior to vaccination N=19 [95% CI]	Total enrolled subjects N=24 [95% CI]	Sero-negative subjects prior to vaccination N=15 [95% CI]	Total enrolled subjects N=15 [95% CI]	Sero-negative subjects prior to vaccination N=7 [95% CI]
Seroprotection rate ¹	92.7% [80.1; 98.5]	91.3% [72.0; 98.9]	51.5% [33.5; 69.2]	31.6% [12.6; 56.6]	83.3% [62.6; 95.3]	73.3% [44.9; 92.2]	66.7% [38.4; 88.2]	28.6% [3.7; 71.0]

¹ seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre $\geq 1:40$

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like		
	>80 years		
	Month 6 after 2 doses of 0.5 ml		Month 6 after 1 dose of 0.5 ml
	Total enrolled subjects N=3 [95% CI]	Seronegative subjects prior to vaccination N=1 [95% CI]	Total enrolled subjects ² N=2 [95% CI]
Seroprotection rate ¹	100% [29.2;100]	100% [2.5;100]	50.0% [1.3;98.7]

¹ seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre $\geq 1:40$

² all subjects seronegative prior to vaccination

Twelve months after the first dose, the seroprotection rate was as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like							
	61-70 years				71-80 years			
	Month 12 after 2 doses of 0.5 ml		Month 12 after 1 dose of 0.5 ml		Month 12 after 2 doses of 0.5 ml		Month 12 after 1 dose of 0.5 ml	
	Total enrolled subjects N=40 [95% CI]	Sero-negative subjects prior to vaccination N=23 [95% CI]	Total enrolled subjects N=33 [95% CI]	Sero-negative subjects prior to vaccination N=19 [95% CI]	Total enrolled subjects N=25 [95% CI]	Sero-negative subjects prior to vaccination N=16 [95% CI]	Total enrolled subjects N=15 [95% CI]	Sero-negative subjects prior to vaccination N=7

								[95% CI]
Seroprotection rate ¹	55.0% [38.5;70.7]	34.8% [16.4;57.3]	39.4% [22.9;57.9]	21.1% [6.1;45.6]	48.0% [27.8;68.7]	25.0% [7.3;52.4]	53.3% [26.6;78.7]	14.3% [0.4;57.9]

¹ seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre $\geq 1:40$

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like		
	>80 years		
	Month 12 after 2 doses of 0.5 ml		Month 12 after 1 dose of 0.5 ml
	Total enrolled subjects N=3 [95% CI]	Seronegative subjects prior to vaccination N=1 [95% CI]	Total enrolled subjects ² N=2 [95% CI]
Seroprotection rate ¹	100% [29.2;100]	100% [2.5;100]	50.0% [1.3;98.7]

¹ seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre $\geq 1:40$

² all subjects seronegative prior to vaccination

The neutralising antibody responses in subjects >60 years were as follows:

Serum neutralising antibody	Immune response to A/Netherlands/602/9 (H1N1)v-like ¹					
	After 2 doses of 0.5 ml			After 1 dose of 0.5 ml		
	Day 21 N=22	Day 42 N=22	Month 6 N=22	Day 21 N=18	Day 42 N=18	Month 6 N=18
Vaccine Response Rate ²	68.2% [45.1;86.1]	86.4% [65.1;97.1]	63.6% [40.7;82.8]	33.3% [13.3;59.0]	27.8% [9.7;53.5]	38.9% [17.3;64.3]

¹ antigenically similar to A/California/7/2009 (H1N1)v-like

² percentage of vaccinees who, if initially seronegative reach an antibody titre ≥ 32 1/DIL after vaccination or, if initially seropositive reach an antibody titre ≥ 4 fold the pre-vaccination antibody titre

Paediatric population

Children aged 10-17 years

Two clinical studies evaluated the administration of a half (0.25 ml) dose and a full (0.5 ml) adult dose of Pandemrix in healthy children 10 to 17 years of age. The anti-HA antibody responses 21 days after the first and the second dose were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like							
	Half dose (D-Pan-H1N1-023)				Full dose (D-Pan-H1N1-010)			
	Total subjects ⁴ [95% CI]		Seronegative subjects prior to vaccination [95% CI]		Total subjects ⁴ [95% CI]		Seronegative subjects prior to vaccination [95% CI]	
	Post dose 1 N=54	Post dose 2 N=54	Post dose 1 N=37	Post dose 2 N=37	Post dose 1 N=92	Post dose 2 N=88	Post dose 1 N=59	Post dose 2 N=57
Sero-	98.1%	100%	97.3%	100%	100%	100%	100%	100%

protection rate ¹	[90.1; 100]	[93.4; 100]	[85.8; 99.9]	[90.5; 100]	[96.1; 100]	[95.9; 100]	[93.9; 100]	[93.7; 100]
Sero-conversion rate ²	96.3% [87.3; 99.5]	98.1% [90.1; 100]	97.3% [85.8; 99.9]	100% [90.5; 100]	96.7% [90.8; 99.3]	96.6% [90.4; 99.3]	100% [93.9; 100]	100% [93.7; 100]
Sero-conversion factor ³	48.29 [35.64; 65.42]	107.74 [76.64; 151.45]	67.7 [49.21; 93.05]	187.92 [150.67; 234.38]	72.2 [57.2; 91.2]	139.1 [105.7; 183.1]	99.4 [81.0; 122.1]	249.8 [212.9; 293.2]

¹ seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre $\geq 1:40$; ² seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of $\geq 1:40$, or who were seropositive at pre-vaccination and have a 4-fold increase in titre;

³ seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

⁴ according to protocol

The Day 180 seroprotection rate in the children who had received two half (0.25 ml) doses was 100%.

Twelve months after the first dose, the seroprotection rates in the children who had received two half (0.25 ml) doses were 90.2% and 100% in those who had received two full (0.5 ml) adult doses.

The neutralising antibody responses were as follows:

Serum neutralising antibody	Immune response to A/Netherlands/602/9 (H1N1)v-like ¹					
	Half dose			Full dose		
	Post dose 1 N=13	Post dose 2 N=14	Month 6 N=13	Post dose 1 N=30	Post dose 2 N=29	Month 12 N=28
Vaccine Response Rate ²	69.2% [38.6;90.9]	100% [76.8;100]	92.3% [64.0;99.8]	86.7% [69.3;96.2]	100% [88.1;100]	89.3% [71.8;97.7]

¹ antigenically similar to A/California/7/2009 (H1N1)v-like

² percentage of vaccinees who, if initially seronegative reach an antibody titre ≥ 32 1/DIL after vaccination or, if initially seropositive reach an antibody titre ≥ 4 fold the pre-vaccination antibody titre

Children aged 3 to 9 years

In two clinical studies in which children aged 3 to 9 years old received two 0.25 ml doses (half adult dose) or two 0.5 ml doses (adult dose) of Pandemrix, the anti-HA antibody responses 21 days after the first and the second dose were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like					
	3-5 years					
	Half adult dose (D-Pan-H1N1-023)				Adult dose ⁵ (D-Pan-H1N1-010)	
	Total subjects ⁴ N=28 [95% CI]		Seronegative subjects prior to vaccination N=26 [95% CI]		Total subjects ⁴ N=51 [95% CI]	
	Post dose 1	Post dose 2	Post dose 1	Post dose 2	Post dose 1	Post dose 2

Seroprotection rate ¹	100% [87.7;100]	100% [87.7;100]	100% [86.8;100]	100% [86.8;100]	100% [93.0;100]	100% [93.0;100]
Seroconversion rate ²	100% [87.7;100]	100% [87.7;100]	100% [86.8;100]	100% [86.8;100]	100% [93.0;100]	100% [93.0;100]
Seroconversion factor ³	33.62 [26.25;43.05]	237.68 [175.28;322.29]	36.55 [29.01;46.06]	277.31 [223.81;343.59]	49.1 [41.9;57.6]	384.9 [336.4;440.3]

¹ seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre $\geq 1:40$; ²seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of $\geq 1:40$, or who were seropositive at pre-vaccination and have a 4-fold increase in titre;

³seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

⁴according to protocol

⁵all subjects seronegative prior to vaccination

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like							
	6-9 years							
	Half adult dose (D-Pan-H1N1-023)				Adult dose (D-Pan-H1N1-010)			
	Total subjects ⁴ N=30 [95% CI]		Seronegative subjects prior to vaccination N=29 [95% CI]		Total subjects ⁴ N=55 [95% CI]		Seronegative subjects prior to vaccination N=48 [95% CI]	
	Post dose 1	Post dose 2	Post dose 1	Post dose 2	Post dose 1	Post dose 2	Post dose 1	Post dose 2
Seroprotection rate ¹	100% [88.4; 100]	100% [88.4; 100]	100% [88.1; 100]	100% [88.1; 100]	100% [93.5; 100]	100% [93.5; 100]	100% [92.6; 100]	100% [92.6; 100]
Seroconversion rate ²	100% [88.4; 100]	100% [88.4; 100]	100% [88.1; 100]	100% [88.1; 100]	100% [93.5; 100]	100% [93.5; 100]	100% [92.6; 100]	100% [92.6; 100]
Seroconversion factor ³	36.33 [27.96; 47.22]	185.25 [142.09; 241.52]	37.7 [28.68; 48.71]	196.81 [154.32; 251.00]	59.0 [48.3; 72.0]	225.7 [182.7; 278.2]	61.7 [49.9; 76.3]	283.2 [246.0; 326.0]

¹ seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre $\geq 1:40$; ²seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of $\geq 1:40$, or who were seropositive at pre-vaccination and have a 4-fold increase in titre;

³seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

⁴according to protocol

The Day 180 seroprotection rate in the children who had received two half (0.25 ml) doses was 100% in both age groups. Twelve months after the first dose, the seroprotection rate was 85% in both age groups. In the children who had received two adult (0.5 ml) doses, the seroprotection rates twelve months after the first dose were 100% for children aged 3-5 years and 98.0% for those aged 6-9 years.

The neutralising antibody responses were as follows:

Serum neutralising antibody	Immune response to A/Netherlands/602/9 (H1N1)v-like ¹
-----------------------------	--

	3-5 years					
	Half adult dose			Adult dose		
	Post dose 1 N=16	Post dose 2 N=15	Month 6 N=16	Post dose 1 N=32	Post dose 2 N=29	Month 12 N=24
Vaccine Response Rate ²	50.0% [24.7; 75.3]	100% [78.2; 100]	100% [79.4; 100]	81.3% [63.6; 92.8]	100% [88.1; 100]	100% [85.8; 100]

¹antigenically similar to A/California/7/2009 (H1N1)v-like

²percentage of vaccinees who, if initially seronegative reach an antibody titre ≥ 32 1/DIL after vaccination or, if initially seropositive reach an antibody titre ≥ 4 fold the pre-vaccination antibody titre

Serum neutralising antibody	Immune response to A/Netherlands/602/9 (H1N1)v-like ¹					
	6-9 years					
	Half adult dose			Adult dose		
	Post dose 1 N=14	Post dose 2 N=15	Month 6 N=15	Post dose 1 N=37	Post dose 2 N=37	Month 12 N=31
Vaccine Response Rate ²	71.4% [41.9; 91.6]	100% [78.2; 100]	93.3% [68.1; 99.8]	86.7% [69.3; 96.2]	100% [88.1; 100]	96.8% [83.3; 99.1]

¹antigenically similar to A/California/7/2009 (H1N1)v-like

²percentage of vaccinees who, if initially seronegative reach an antibody titre ≥ 32 1/DIL after vaccination or, if initially seropositive reach an antibody titre ≥ 4 fold the pre-vaccination antibody titre

Children aged 6-35 months

In a clinical study (D-Pan-H1N1-009) in healthy children 6 months to 35 months of age (stratified in ranges from 6 to 11, 12 to 23 and 24-35 months of age) the anti-HA antibody responses 21 days after a first and a second half adult dose (i.e. 0.25 ml) or adult dose (i.e. 0.5 ml) of Pandemrix were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like							
	6-11 months							
	Half adult dose				Adult dose			
	Total subjects ⁴ [95% CI]		Seronegative subjects prior to vaccination [95% CI]		Total subjects ⁴ [95% CI]		Seronegative subjects prior to vaccination [95% CI]	
	Post dose 1	Post dose 2	Post dose 1	Post dose 2	Post dose 1	Post dose 2	Post dose 1	Post dose 2
	N=34	N = 32	N=30	N=28	N=15	N=15	N=14	N=14
Sero-protection rate ¹	100% [89.7; 100]	100% [89.1; 100]	100% [88.4; 100]	100% [87.7; 100]	100% [78.2; 100]	100% [78.2; 100]	100% [76.8; 100]	100% [76.8; 100]
Sero-conversion rate ²	97.1% [84.7; 99.9]	100% [89.1; 100]	100% [88.4; 100]	100% [87.7; 100]	100% [78.2; 100]	100% [78.2; 100]	100% [76.8; 100]	100% [76.8; 100]
Sero-conversion factor ³	48.12 [34.34; 67.42]	276.14 [164.23; 455.99]	64.0 [52.3; 78.3]	441.3 [365.7; 532.6]	46.29 [38.83; 59.80]	370;48 [217,97; 629,69]	49.9 [40.3; 61.9]	452.4 [322.4; 634.6]

¹ seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre $\geq 1:40$; ²seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of $\geq 1:40$, or who were seropositive at pre-vaccination and have a 4-fold increase in titre;

³seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

⁴according to protocol

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like							
	12-23 months							
	Half adult dose				Adult dose			
	Total subjects ⁴ [95% CI]		Seronegative subjects prior to vaccination [95% CI]		Total subjects ⁴ [95% CI]		Seronegative subjects prior to vaccination [95% CI]	
	Post dose 1	Post dose 2	Post dose 1	Post dose 2	Post dose 1	Post dose 2	Post dose 1	Post dose 2
	N=34	N= 32	N=33	N=31	N=16	N=17	N=15	N=16
Sero-protection rate ¹	100% [89.7; 100]	100% [89.1; 100]	100% [89.4; 100]	100% [88.8; 100]	100% [79.4; 100]	100% [80.5; 100]	100% [78.2; 100]	100% [79.4; 100]
Sero-conversion rate ²	100% [89.7; 100]	100% [89.1; 100]	100% [89.4; 100]	100% [88.8; 100]	100% [79.4; 100]	100% [80.5; 100]	100% [78.2; 100]	100% [79.4; 100]
Sero-conversion factor ³	63.37 [48.13; 83.43]	386.45 [308.54; 484.02]	66.7 [51.4; 86.7]	404.8 [327.8; 500.0]	64.06 [38.55; 106.44]	472.16 [343.74; 648.57]	75.3 [50.3; 112.5]	523.2 [408.5; 670.1]

¹ seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre $\geq 1:40$; ²seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of $\geq 1:40$, or who were seropositive at pre-vaccination and have a 4-fold increase in titre;

³seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

⁴according to protocol

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like					
	24-35 months					
	Half adult dose ⁴		Adult dose			
	Total subjects ⁵ [95% CI]		Total subjects ⁵ [95% CI]		Seronegative subjects prior to vaccination [95% CI]	
	Post dose 1	Post dose 2	Post dose 1	Post dose 2	Post dose 1	Post dose 2
	N=33	N= 33	N=16	N=16	N=12	N=12
Sero-protection rate ¹	100% [89.4; 100]	100% [89.4; 100]	100% [79.4;100]	100% [79.4;100]	100% [73.5;100]	100% [73.5;100]
Sero-conversion rate ²	100% [89.4; 100]	100% [89.4; 100]	93.8 [69.8;99.8]	100% [79.4;100]	100% [73.5;100]	100% [73.5;100]
Sero-conversion factor ³	52.97 [42.08;66.68]	389.64 [324.25; 468.21]	33.44 [18.59;60.16]	189.16 [83.80; 427.01]	55.4 [39.8;77.2]	406.4 [296.2;557.4]

¹ seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre $\geq 1:40$; ²seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of $\geq 1:40$, or who were seropositive at pre-vaccination and have a 4-fold increase in titre;

³seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

⁴all subjects seronegative prior to vaccination

⁵according to protocol

Twelve months after the first dose, the seroprotection rate was 100% in all age groups and dosage groups.

The clinical relevance of the haemagglutination inhibition (HI) titre $\geq 1:40$ in children is unknown.

The neutralising antibody responses were as follows:

Serum neutralising antibody	Immune response to A/Netherlands/602/9 (H1N1)v-like ¹					
	6-11 months					
	Half dose			Adult dose		
	Post dose 1 N=28	Post dose 2 N=28	Month 12 N=22	Post dose 1 N=14	Post dose 2 N=14	Month 12 N=10
Vaccine Response Rate ²	57.1% [37.2; 75.5]	96.4% [81.7; 99.9]	86.4% [65.1; 97.1]	57.1% [28.9; 82.3]	100% 76.8; 100]	100% [69.2; 100]

¹antigenically similar to A/California/7/2009 (H1N1)v-like

²percentage of vaccinees who, if initially seronegative reach an antibody titre ≥ 32 1/DIL after vaccination or, if initially seropositive reach an antibody titre ≥ 4 fold the pre-vaccination antibody titre

Serum neutralising antibody	Immune response to A/Netherlands/602/9 (H1N1)v-like ¹					
	12-23 months					
	Half dose			Adult dose		
	Post dose 1 N=14	Post dose 2 N=16	Month 12 N=13	Post dose 1 N=7	Post dose 2 N=8	Month 12 N=7
Vaccine Response Rate ²	57.1% [28.9;82.3]	100% [79.4;100]	92.3% [64.0;99.8]	71.4% [29.0;96.3]	100% [63.1;100]	100% [59.0;100]

¹antigenically similar to A/California/7/2009 (H1N1)v-like

²percentage of vaccinees who, if initially seronegative reach an antibody titre ≥ 32 1/DIL after vaccination or, if initially seropositive reach an antibody titre ≥ 4 fold the pre-vaccination antibody titre

Serum neutralising antibody	Immune response to A/Netherlands/602/9 (H1N1)v-like ¹					
	24-35 months					

	Half dose			Adult dose		
	Post dose 1 N=17	Post dose 2 N=17	Month 12 N=14	Post dose 1 N=8	Post dose 2 N=7	Month 12 N=5
Vaccine Response Rate ²	58.8% [32.9;81.6]	100% [80.5;100]	100% [76.8;100]	62.5% [24.5;91.5]	100% [59.0;100]	100% [47.8;100]

¹antigenically similar to A/California/7/2009 (H1N1)v-like

²percentage of vaccinees who, if initially seronegative reach an antibody titre ≥ 32 1/DIL after vaccination or, if initially seropositive reach an antibody titre ≥ 4 fold the pre-vaccination antibody titre

The European Medicines Agency has deferred the obligation to submit the results of studies with

Pandemrix in one or more subsets of the paediatric population in the prevention of influenza infection (see section 4.2 for information on paediatric use).

Information from non-clinical studies:

The ability to induce protection against homologous and heterologous vaccine strains was assessed non-clinically using ferret challenge models.

In each experiment, four groups of six ferrets were immunized intramuscularly with an AS03 adjuvanted vaccine containing HA derived from H5N1/A/Vietnam/1194/04 (NIBRG-14). Doses of 15, 5, 1.7 or 0.6 micrograms of HA were tested in the homologous challenge experiment, and doses of 15, 7.5, 3.8 or 1.75 micrograms of HA were tested in the heterologous challenge experiment. Control groups included ferrets immunized with adjuvant alone, non-adjuvanted vaccine (15 micrograms HA) or phosphate buffered saline solution. Ferrets were vaccinated on days 0 and 21 and challenged by the intra-tracheal route on day 49 with a lethal dose of either H5N1/A/Vietnam/1194/04 or heterologous H5N1/A/Indonesia/5/05. Of the animals receiving adjuvanted vaccine, 87% and 96% were protected against the lethal homologous or heterologous challenge, respectively. Viral shedding into the upper respiratory tract was also reduced in vaccinated animals relative to controls, suggesting a reduced risk of viral transmission. In the unadjuvanted control group, as well as in the adjuvant control group, all animals died or had to be euthanized as they were moribund, three to four days after the start of challenge.

Additional information is available from the studies conducted with a vaccine similar in composition to Pandemrix but containing antigen derived from H5N1 viruses. Please consult the Product Information of Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data obtained with the mock-up vaccine using a H5N1 vaccine strain reveal no special hazard for humans based on conventional studies of safety pharmacology, acute and repeated dose toxicity, local tolerance, female fertility, embryo-fetal and postnatal toxicity (up to the end of the lactation period).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Suspension vial:

Sodium chloride
Disodium phosphate
Potassium dihydrogen phosphate
Potassium chloride
Magnesium chloride
Polysorbate 80
Thiomersal
Octoxynol 10
Water for injections

Emulsion vial:

Sodium chloride
Disodium phosphate
Potassium dihydrogen phosphate
Potassium chloride
Water for injections

For adjuvants, see section 2.

6.2 Incompatibilities

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

6.3 Shelf life

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

After mixing, the vaccine should be used within 24 hours. Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

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 mixing of the medicinal product, see section 6.3.

6.5 Nature and contents of container

One pack containing:

- one pack of 50 vials (type I glass) of 2.5 ml suspension with a stopper (butyl rubber).
- two packs of 25 vials (type I glass) of 2.5 ml emulsion with a stopper (butyl rubber).

The volume after mixing 1 vial of suspension (2.5 ml) with 1 vial of emulsion (2.5 ml) corresponds to 10 doses of vaccine (5 ml).

6.6 Special precautions for disposal and other handling

Pandemrix consists of two containers:
Suspension: multidose vial containing the antigen,
Emulsion: multidose vial containing the adjuvant.

Prior to administration, the two components should be mixed.

Instructions for mixing and administration of the vaccine:

1. Before mixing the two components, the emulsion (adjuvant) and suspension (antigen) should be brought to room temperature (allow a minimum of 15 minutes); each vial should be shaken and inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed (including rubber particles from the stopper), discard the vaccine.
2. The vaccine is mixed by withdrawing the entire contents of the vial containing the adjuvant by means of a 5 ml syringe and by adding it to the vial containing the antigen. It is recommended to equip the syringe with a 23-G needle. However, in the case this needle size would not be available, a 21-G needle might be used. The vial containing the adjuvant should be maintained in upside down position to facilitate the withdrawal of the full content.
3. After the addition of the adjuvant to the antigen, the mixture should be well shaken. The mixed vaccine is a whitish emulsion. In the event of other variation being observed, discard the vaccine.
4. The volume of the Pandemrix vial after mixing is at least 5 ml. The vaccine should be administered in accordance with the recommended posology (see section 4.2).
5. The vial should be shaken prior to each administration and inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed (including rubber particles from the stopper), discard the vaccine.
6. Each vaccine dose of 0.5 ml (full dose) or 0.25 ml (half dose) is withdrawn into a 1 ml syringe for injection and administered intramuscularly. It is recommended to equip the syringe with a needle gauge not larger than 23-G.
7. After mixing, use the vaccine within 24 hours. The mixed vaccine can either be stored in a refrigerator (2°C - 8°C) or at room temperature not exceeding 25°C. If the mixed vaccine is stored in a refrigerator, it should be brought to room temperature (allow a minimum of 15 minutes) before each withdrawal.

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

7. MANUFACTURER

GlaxoSmithKline Biologicals S.A., Rixensart, Belgium
Rixensart, Belgium

8. LICENSE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva

9. LICENSE NUMBER

146-67-33072