ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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 to yellowish homogeneous milky liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of influenza caused by A (H1N1)v 2009 virus. 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 sections 4.4 and 4.8).

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 ≥38°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 (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥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		Febrile convulsions
	Very rare[1]	Narcolepsywith or without cataplexy (see section 4.4)
		Somnolence[2]
Skin and subcutaneous tissue		Angioedema, generalised skin reactions,

disorders		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

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

[2]Reported 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 via the national reporting system listed in Appendix V.

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 1st dose		21 days after 2nd dose		21 days after 1st dose		21 days after 2nd 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 ≥1:40;
[2]seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥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	Total enrolled subjects N=67 [95% CI]	Sero-negative subjects prior to vaccination N=43	Total enrolled subjects N=51 [95% CI]	Sero-negative subjects prior to vaccination N=32

		[95% CI]		[95% CI]		[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 ≥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 ≥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 N=22	Day 42 N=22	Month 6 N=22	Day 21 N=17	Day 42 N=17	Month 6 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]

[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

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 1st dose		21 days after 2nd dose		21 days after 1st dose		21 days after 2nd 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]

[1] seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40;
[2]seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥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.

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like			
	>80 years			
	21 days after 1st dose		21 days after 2nd 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 factor[3]	18.4 [4.3;78.1]	17.95 [0.55;582.25]	25.49 [0.99;654.60]	64.0

[1] seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40;
[2]seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥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 vaccina-tion N=7 [95% CI]
Seropro-tection 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 ≥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 ≥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 vaccina-tion N=7 [95% CI]
Seropro-tection 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 ≥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 ≥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-protection rate[1]	98.1% [90.1; 100]	100% [93.4; 100]	97.3% [85.8; 99.9]	100% [90.5; 100]	100% [96.1; 100]	100% [95.9; 100]	100% [93.9; 100]	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 ≥1:40;
[2]seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥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 ≥1:40;
[2]seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥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
[5]all 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 ≥1:40;
[2]seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥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% 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 neutrali-sing 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]

[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

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]

[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 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]	Seronegative subjects	Total subjects[4]	Seronegative subjects

	[95% CI]		prior to vaccination [95% CI]		[95% CI]		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 ≥1:40;
[2]seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥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

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 ≥1:40;
[2]seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥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

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 ≥1:40;
[2]seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥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]all subjects seronegative prior to vaccination
[5]according 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 ≥1:40 in children is unknown.

The neutralising antibody responses were as follows:

Serum neutrali-sing 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]

[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

Serum neutrali-sing 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]

[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

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]

[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

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:
Polysorbate 80
Octoxynol 10
Thiomersal
Sodium chloride (NaCl)
Disodium hydrogen phosphate (Na_2HPO_4)
Potassium dihydrogen phosphate (KH_2PO_4)
Potassium chloride (KCl)
Magnesium chloride ($MgCl_2$)
Water for injections

Emulsion vial:
Sodium chloride (NaCl)
Disodium hydrogen phosphate (Na_2HPO_4)
Potassium dihydrogen phosphate (KH_2PO_4)
Potassium chloride (KCl)
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

2 years.

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 to yellowish homogeneous milky liquid 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. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/452/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 May 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

GlaxoSmithKline Biologicals
Branch of SmithKline Beecham Pharma GmbH & Co. KG
Zirkustraße 40, D-01069 Dresden
Germany

Name and address of the manufacturer responsible for batch release

GlaxoSmithKline Biologicals S.A.
89, rue de l'Institut
B-1330 Rixensart
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached

If the dates for submission of a PSUR and the update of a RMP coincide, they can submit at the same time.

- **Additional risk minimisation measures**

The MAH shall agree with Member States to measures facilitating the identification and traceability of the A/H1N1 vaccine administered to each patient, in order to minimise medication errors and aid patients and health care professionals to report adverse reactions. This may include the provision by the MAH of stickers with invented name and batch number with each pack of the vaccine.

The MAH shall agree with Member States on mechanisms allowing patients and health care professionals to have continuous access to updated information regarding Pandemrix.

The MAH shall agree with Member States on the provision of a targeted communication to healthcare professionals which should address the following:

- The correct way to prepare the vaccine prior to administration.
- Adverse events to be prioritised for reporting, i.e. fatal and life-threatening adverse reactions, unexpected severe adverse reactions, adverse events of special interest (AESI).
- The minimal data elements to be transmitted in individual case safety reports in order to facilitate the evaluation and the identification of the vaccine administered to each subject, including the invented name, the vaccine manufacturer and the batch number.
- If a specific notification system has been put in place, how to report adverse reactions.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due Date
Conduct a retrospective epidemiological study in Canada (Quebec) and follow-up cases to assess any atypical or differential clinical course and prognosis in any vaccinated vs. non-vaccinated subjects: - Re-analysis of the dataset after exclusion of symptomatic controls after 1 year follow-up (if applicable); and description of the clinical follow-up of cases for 2 years.	December 2014
Conduct non-clinical (including mechanistic) studies in order to elucidate the role of the vaccine and its adjuvant on the association between Pandemrix and narcolepsy: - If deep sequencing approach is proven feasible: o identify T cell signature from narcoleptic patients and, if identified, verify if signature is found in CD4 T cells from healthy vaccinees o if identified, verify if T cell signature is detected in influenza-specific CD4 T cells from narcoleptic patients - Establish influenza-specific T cell lines to evaluate potential cross-reactivity with hypocretin peptides, with identified DQ*0602 binders and with additional proteins using T2 cells as antigen-presenting cells - Conduct a study in cotton rats to evaluate the potential impact of Pandemrix vaccination/H1N1v infection on the blood-brain-barrier integrity and CNS inflammation/damage. - 'Evaluate the potential for immunological differences between Pandemrix and Arepanrix H1N1 using antibody avidity analysis and phage display-assisted epitope mapping from clinical serum samples obtained before and at Day 21 after vaccination from clinical studies in which the two vaccines were compared.	June 2014 December 2014 December 2014 June 2014 December 2014

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PACK CONTAINING 1 PACK OF 50 VIALS OF SUSPENSION AND 2 PACKS OF 25 VIALS OF EMULSION

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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*

AS03 adjuvant composed of squalene, DL-α-tocopherol and polysorbate 80

* haemagglutinin

3. LIST OF EXCIPIENTS

Polysorbate 80
Octoxynol 10
Thiomersal
Sodium chloride (NaCl)
Disodium hydrogen phosphate (Na_2HPO_4)
Potassium dihydrogen phosphate (KH_2PO_4)
Potassium chloride (KCl)
Magnesium chloride ($MgCl_2$)
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension and emulsion for emulsion for injection

50 vials: suspension (antigen)
50 vials: emulsion (adjuvant)
The volume after mixing 1 vial of suspension (2.5 ml) with 1 vial of emulsion (2.5 ml) corresponds to **10 doses** of 0.5 ml vaccine

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Shake before use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Suspension and emulsion to be mixed before administration

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/452/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PACK OF 50 VIALS OF SUSPENSION (ANTIGEN)

1. NAME OF THE MEDICINAL PRODUCT

Suspension for emulsion for injection for Pandemrix
Influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Split influenza virus, inactivated, containing antigen* equivalent to

3.75 micrograms haemagglutinin/dose
*Antigen: A/California/07/2009 (H1N1) derived strain used NYMCX-179A

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Antigen suspension for injection
50 vials: suspension
2.5 ml per vial.
After mixing with adjuvant emulsion: **10 doses** of 0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Shake before use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Suspension to be exclusively mixed with adjuvant emulsion before administration

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GSK Biologicals, Rixensart - Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/452/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PACK OF 25 VIALS OF EMULSION (ADJUVANT)

1. NAME OF THE MEDICINAL PRODUCT

Emulsion for emulsion for injection for Pandemrix

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients:
Sodium chloride
Disodium hydrogen phosphate
Potassium dihydrogen phosphate
Potassium chloride
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Adjuvant emulsion for injection
25 vials: emulsion
2.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Shake before use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Emulsion to be exclusively mixed with antigen suspension before administration

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GSK Biologicals, Rixensart - Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/452/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SUSPENSION VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Antigen suspension for Pandemrix
Influenza vaccine
A/California/07/2009 (H1N1) derived strain used NYMC X-179A
I.M.

2. METHOD OF ADMINISTRATION

Mix with adjuvant emulsion before use

3. EXPIRY DATE

EXP
After mixing: Use within 24 hours and do not store above 25°C.
Date and time of mixing:

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 ml
After mixing with adjuvant emulsion: 10 doses of 0.5 ml

6. OTHER

Storage (2ºC-8ºC), do not freeze, protect from light

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

EMULSION VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Adjuvant emulsion for Pandemrix
I.M.

2. METHOD OF ADMINISTRATION

Mix into Antigen suspension before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 ml

6. OTHER

Storage (2ºC-8ºC), do not freeze, protect from light

B. PACKAGE LEAFLET

Package leaflet: Information for the user

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

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This vaccine has been prescribed for you only. Do not pass it on to others.
- If you get any of side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Pandemrix is and what it is used for
2. What you need to know before you receive Pandemrix
3. How Pandemrix is given
4. Possible side effects
5. How to store Pandemrix
6. Contents of the pack and other information

1. What Pandemrix is and what it is used for

What Pandemrix is and what it is used for

Pandemrix is a vaccine to prevent influenza (flu) caused by A(H1N1)v 2009 virus.
Your doctor will normally recommend a different vaccine (annual trivalent/quadrivalent influenza vaccine) instead of Pandemrix, but if the trivalent/quadrivalent vaccines are not available Pandemrix may still be an option if you need protection against A(H1N1)v influenza (see Take special care with Pandemrix).

How Pandemrix works

When a person is given the vaccine, the immune system (the body's natural defence system) will produce its own protection (antibodies) against the disease. None of the ingredients in the vaccine can cause flu.

2. What you need to know before you receive Pandemrix

Pandemrix should not be given:

- if you have previously had a sudden life-threatening allergic reaction to any ingredient of this vaccine (listed in section 6) or to any of the substances that may be present in trace amounts as follows: egg and chicken protein, ovalbumin, formaldehyde, gentamicin sulphate (antibiotic) or sodium deoxycholate. Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.
- if you have a severe infection with a high temperature (over 38°C). If this applies to you then your vaccination will usually be postponed until you are feeling better. A minor infection such as a cold should not be a problem, but your doctor or nurse will advise whether you could still be vaccinated with Pandemrix.

If you are not sure, talk to your doctor or nurse before having this vaccine.

Warnings and precautions

Talk to your doctor or nurse before you receive Pandemrix:

- if you have had any allergic reaction other than a sudden life-threatening allergic reaction to any ingredient contained in this vaccine (listed in section 6), to thiomersal, to egg and chicken protein, ovalbumin, formaldehyde, gentamicin sulphate (antibiotic) or to sodium deoxycholate. .
- if you are having a blood test to look for evidence of infection with certain viruses. In the first few weeks after vaccination with Pandemrix the results of these tests may not be correct. Tell the doctor requesting these tests that you have recently been given Pandemrix.
- if you have a bleeding problem or bruise easily.

In any of these cases, TELL YOUR DOCTOR OR NURSE, as vaccination may not be recommended, or may need to be delayed.

Excessive sleepiness during the day, often at the wrong times (a long-term condition called narcolepsy), has been reported very rarely after vaccination with Pandemrix in several European countries. Narcolepsy can occur with or without sudden muscle weakness that can cause falls (a condition called cataplexy).

Children and adolescents

If your child receives the vaccine, you should be aware that the side effects may be more intense after the second dose, especially temperature over 38°C. Therefore monitoring of temperature and measures to lower the temperature (such as giving paracetamol or other medicines that lower fever) after each dose are recommended.

Fainting can occur (mostly in adolescents) following, or even before, any needle injection. Therefore tell the doctor or nurse if you fainted with a previous injection.

Other medicines and Pandemrix
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines or have recently received any other vaccine.

Pandemrix can be given at the same time as seasonal influenza vaccines that do not contain an adjuvant.

Persons who have received a seasonal influenza vaccine that does not contain an adjuvant may receive Pandemrix after an interval of at least three weeks.

There is no information on administration of Pandemrix with other vaccines. However, if this cannot be avoided, the vaccines should be injected into separate limbs. In such cases, you should be aware that the side effects may be more intense.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you receive this vaccine.

Driving and using machines
Some effects mentioned under section 4. “Possible side effects” may affect the ability to drive or use machines.

Pandemrix contains thiomersal
Pandemrix contains thiomersal as a preservative and it is possible that you may experience an allergic reaction. Tell your doctor if you have any known allergies.

Pandemrix contains sodium and potassium
This medicinal product contains less than 1 mmol sodium (23 mg) and less than 1 mmol of potassium (39 mg) per dose, i.e. essentially sodium- and potassium-free.

3. How Pandemrix is given

Your doctor or nurse will administer the vaccine in accordance with official recommendations.

Adults, including the elderly
A dose (0.5 ml) of the vaccine will be given.
Clinical data 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 second dose.

Use in children and adolescents

Children from the age of 10 years onwards
A dose (0.5 ml) of the vaccine will be given.
Clinical data 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 second dose.

Children from 6 months to 9 years of age
A dose (0.25 ml) of the vaccine will be given.
If a second dose of 0.25 ml is given this will be administered at least three weeks after the first dose.

Children aged less than 6 months of age
Vaccination is currently not recommended in this age group.

The vaccine will be injected into a muscle (usually in the upper arm).

If you have any further questions on the use of this vaccine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this vaccine can cause side effects, although not everybody gets them.

Allergic reactions:

Allergic reactions may occur following vaccination, in rare cases leading to shock. Doctors are aware of this possibility and have emergency treatment available for use in such cases.

Other side effects:

The side effects listed below have occurred with Pandemrix in clinical studies in adults, including the elderly.

Very common: may affect more than 1 in 10 people
- Headache
- Tiredness
- Pain and swelling at the injection site

- Shivering
- Increased sweating
- Aching muscles, joint pain

Common: may affect up to 1 in 10 people
- Redness and itching at the injection site
- Fever
- Feeling sick, diarrhoea, vomiting, stomach pain

Uncommon: may affect up to 1 in 100 people
- A hard lump and warmth at the injection site
- Swollen glands in the neck, armpit or groin
- Tingling or numbness of the hands or feet
- Sleeplessness
- Dizziness
- Itching, rash
- Generally feeling unwell
- Flu-like symptoms

These side effects usually disappear within 1-2 days without treatment. If they persist, CONSULT YOUR DOCTOR.

Additional side effects in children and adolescents

Children aged 10-17 years

The side effects listed above have also been observed with similar frequencies in clinical studies in children 10 to 17 years of age, except for redness at the injection site which was very common and sweating which was common.

Children aged 3-9 years

In children 3 to 9 years of age who received two 0.25 ml doses of Pandemrix (H1N1) the side effects reported were similar to those reported in adults, except for redness at the injection site and gastrointestinal symptoms which were very common and shivering and sweating which were common. In addition, fever was very common in children aged 3-5 years. Some side effects (including local redness and fever) occurred more frequently after the second dose compared to the first dose.

Children aged 6-35 months

In children aged 6-35 months who received two doses of 0.25 ml of Pandemrix (H1N1), there was an increase in reports of pain, redness and swelling at the injection site as well as fever (>38°C), drowsiness, irritability and loss of appetite after the second dose compared to the first dose. All these side effects were reported very commonly after each dose.

The side effects listed below have happened after Pandemrix (H1N1)v came on the market:

- Allergic reactions leading to a dangerous decrease of blood pressure, which, if untreated, may lead to shock. Doctors are aware of this possibility and have emergency treatment available for use in such cases.
- Generalised skin reactions including facial swelling and urticaria (hives)
- Fits due to fever
- A long-term condition with excessive daytime sleepiness (narcolepsy), with or without sudden weakness (cataplexy), which may lead to falls without loss of consciousness
- Short-term sleepiness following vaccination

- Reactions at the injection site such as pain, redness, bruising, swelling and heat (inflammation), hard lump (mass)

The side effects listed below have occurred in the days or weeks after vaccination with vaccines given routinely every year to prevent flu. They may also happen with Pandemrix.

Rare: may affect up to 1 in 1,000 people
- Severe stabbing or throbbing pain along one or more nerves
- Low blood platelet count which can result in bleeding or bruising

Very rare: may affect up to 1 in 10,000 people
- Vasculitis (inflammation of the blood vessels which can cause skin rashes, joint pain and kidney problems)
- Neurological disorders such as encephalomyelitis (inflammation of the central nervous system), neuritis (inflammation of nerves) and a type of paralysis known a Guillain-Barré Syndrome

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Pandemrix

Keep this vaccine out of the sight and reach of children.

Before the vaccine is mixed:
Do not use the suspension and the emulsion after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).
Store in the original package in order to protect from light.
Do not freeze.

After the vaccine is mixed:
After mixing, use the vaccine within 24 hours and do not store above 25°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Pandemrix contains

- Active substance:
  Split influenza virus, inactivated, containing antigen* equivalent to:

  A/California/07/2009 (H1N1) derived strain used NYMC X-179A 3.75 micrograms** per 0.5 ml dose

  *propagated in eggs
  **expressed in microgram haemagglutinin

- Adjuvant:

The vaccine contains an 'adjuvant' AS03 to stimulate a better response. This adjuvant contains squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams).

- Other ingredients:
  The other ingredients are: polysorbate 80, octoxynol 10, thiomersal, sodium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride, magnesium chloride, water for injections

What Pandemrix looks like and contents of the pack

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

Prior to administration, the two components should be mixed. The mixed vaccine is a whitish to yellowish homogeneous milky liquid emulsion.

One pack of Pandemrix consists of:
- one pack containing 50 vials of 2.5 ml suspension (antigen)
- two packs containing 25 vials of 2.5 ml emulsion (adjuvant)

Marketing Authorisation Holder and Manufacturer

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {MM/YYYY}.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

The following information is intended for healthcare professionals only:

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 to yellowish homogeneous milky liquid 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 3 “How Pandemrix is given”).
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.

The vaccine should not be administered intravascularly.

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