

Attachment 1: Product information for Pandemrix H1N1 pandemic influenza vaccine. Influenza virus haemagglutinin (A/California/7/2009(H1N1)v-like strain). GlaxoSmithKline Australia Pty Ltd. PM-2010-02995-3-2 Final 12 February 2013. This Product Information was approved at the time this AusPAR was published.

PANDEMRIX™ H1N1 PRODUCT INFORMATION

Pandemic influenza vaccine (split virion, inactivated, AS03 adjuvanted)

NAME OF THE MEDICINE

PANDEMRIX H1N1, emulsion and suspension for emulsion for injection.

Pandemic influenza vaccine (split virion, inactivated, AS03 adjuvanted).

DESCRIPTION

Each 0.5mL vaccine dose contains 3.75 micrograms¹ of antigen² of A/California/7/2009 (H1N1)v-like strain and is adjuvanted with AS03³.

¹haemagglutinin

²propagated in eggs

³The GlaxoSmithKline proprietary AS03 adjuvant system is composed of squalene (10.68 milligrams), DL- α -tocopherol (11.86 milligrams) and polysorbate 80 (4.85 milligrams)

This vaccine complies with the World Health Organisation (WHO) recommendation for the pandemic.

Each 0.5mL vaccine dose also contains the excipients Polysorbate 80, Octoxinol 10, Thiomersal, Sodium Chloride, Disodium hydrogen phosphate, Potassium dihydrogen phosphate, Potassium Chloride and Magnesium chloride. The vaccine may also contain the following residues: egg residues including ovalbumin, gentamicin sulfate, formaldehyde, sucrose and sodium deoxycholate.

CLINICAL TRIALS

This section describes the clinical experience with *PANDEMRIX* H1N1 after a single dose in healthy adults aged 18 years and older and the mock-up vaccines (Pandemrix H5N1) following a two-dose administration.

Mock-up vaccines contain influenza antigens that are different from those in the currently circulating influenza viruses. These antigens can be considered as “novel” antigens and simulate a situation where the target population for vaccination is immunologically naïve. Data obtained with the mock-up vaccine will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical efficacy and safety data obtained with mock-up vaccines are relevant for the pandemic vaccines.

Immune response to *PANDEMRIX H1N1*

Adults aged 18-60 years

Two clinical studies (D-Pan H1N1-007 and D-Pan H1N1-008) evaluated the immunogenicity of AS03-adjuvanted vaccine containing 3.75 μ g HA derived from A/California/7/2009 (H1N1)v-like strain in healthy adults aged 18-60 years. In D-Pan H1N1-007 pre-vaccination antibody reciprocal titres $\geq 1:10$ were present in 32.8% of adults and in D-Pan H1N1-008 pre-vaccination antibody reciprocal titres $\geq 1:10$ were present in 36.7% of adults aged 18 to 60 years. The anti-HA antibody responses 21 days after a first dose were as follows:

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anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like strain			
	D-Pan H1N1-007		D-Pan H1N1-008	
	Total enrolled subjects N = 61 [95% CI]	Seronegative subjects prior to vaccination N = 40 [95% CI]	Total enrolled subjects N = 120 [95% CI]	Seronegative subjects prior to vaccination N = 76 [95% CI]
Sero-protection rate ¹	100% [94.1;100]	100% [91.2;100]	97.5% [92.9;99.5]	96.1% [88.9;99.2]
Seroconversion rate ²	96.7% [88.7;99.6]	100% [91.2;100]	95.0% [89.4;98.1]	96.1% [88.9;99.2]
Seroconversion factor ³	43.3 [31.8;59.0]	56.7 [39.9;80.5]	42.15 [33.43;53.16]	50.73 [37.84;68.02]

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

²seroconversion rate: proportion of subjects who are 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

Elderly (>60 years)

Study D-Pan H1N1-008 also evaluated the immunogenicity of AS03-adjuvanted vaccine containing 3.75 μg HA derived from A/California/7/2009 (H1N1)v-like in healthy subjects aged above 60 years. The mean age was 69.1 years. Pre-vaccination antibody reciprocal titres $\geq 1:10$ were present in 42.5% of adults > 60 years. The anti-HA antibody responses 21 days after a first dose were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like strain					
	61 -70 years		71 – 80 years		>80 years	
	Total enrolled subjects N = 75 [95% CI]	Seronegative subjects prior to vaccination N = 43 [95% CI]	Total enrolled subjects N = 40 [95% CI]	Seronegative subjects prior to vaccination N = 23 [95% CI]	Total enrolled subjects N = 5 [95% CI]	Seronegative subjects prior to vaccination N = 3 [95% CI]
Sero-protection rate ¹	88.0% [78.4;94.4]	81.4% [66.6;91.6]	87.5% [73.2;95.8]	82.6% [61.2;95.0]	80.0% [28.4;99.5]	66.7% [9.4;99.2]
Seroconversion rate ²	80.0% [69.2;88.4]	81.4% [66.6;91.6]	77.5% [61.5;89.2]	82.6% [61.2;95.0]	80.0% [28.4;99.5]	66.7% [9.4;99.2]
Seroconversion factor ³	13.5 [10.3;17.7]	20.3 [13.94;28.78]	13.5 [8.6;21.1]	20.67 [11.58;36.88]	18.4 [4.3;78.1]	17.95 [0.55;582.25]

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

²seroconversion rate: proportion of subjects who are 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

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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 a first dose were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like							
	Half dose				Full 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 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 $\geq 1:40$; 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 six months seroprotection rate in the children who had received two half adult doses was 100%.

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

The neutralising antibody responses at days 21 and 42 and at month 6 were 69.2%, 100% and 92.3%, respectively, for those children who received two half adult (0.25 ml) doses (21 days apart). Neutralising antibody responses at days 21 and 42 and at month 12 were 86.7%, 100% and 89.3%, respectively, for those who received two full adult (0.5 ml) doses (21 days apart).

Children aged 3 to 9 years

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

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anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like							
	3-5 years				6-9 years			
	Total subjects ⁴ N=28 [95% CI]		Seronegative subjects prior to vaccination N=26 [95% CI]		Total subjects ⁴ N=30 [95% CI]		Seronegative subjects prior to vaccination N=29 [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
Sero-protection rate ¹	100% [87.7; 100]	100% [87.7; 100]	100% [86.8; 100]	100% [86.8; 100]	100% [88.4; 100]	100% [88.4; 100]	100% [88.1; 100]	100% [88.1; 100]
Sero-conversion rate ²	100% [87.7; 100]	100% [87.7; 100]	100% [86.8; 100]	100% [86.8; 100]	100% [88.4; 100]	100% [88.4; 100]	100% [88.1; 100]	100% [88.1; 100]
Sero-conversion 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]	36.33 [27.96; 47.22]	185.25 [142.09; 241.52]	37.7 [28.68; 48.71]	196.81 [154.32; 251.00]

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 6 months 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.

The neutralising antibody responses at day 21 were 50% and at day 42 and month 6 100% for the children aged 3 to 5 years. For the children aged 6 to 9 years, the neutralising antibody responses were 71.4%, 100% and 93.3% at days 21 and 42 and at month 6, respectively.

Children aged 6-35 months

In a clinical study 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) of Pandemrix were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like							
	6-11 months				12-23 months			
	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=34	N= 32	N=33	N=31
Sero-protection rate ¹	100% [89.7; 100]	100% [89.1; 100]	100% [88.4; 100]	100% [87.7; 100]	100% [89.7; 100]	100% [89.1; 100]	100% [89.4; 100]	100% [88.8; 100]

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Sero-conversion rate ²	97.1% [84.7; 99.9]	100% [89.1; 100]	100% [88.4; 100]	100% [87.7; 100]	100% [89.7; 100]	100% [89.1; 100]	100% [89.4; 100]	100% [88.8; 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]	63.37 [48.13; 83.43]	386.45 [308.54; 484.02]	66.7 [51.4; 86.7]	404.8 [327.8; 500.0]

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

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like 24-35 months ⁴	
	Total subjects ⁵ [95% CI]	
	Post dose 1 N=33	Post dose 2 N= 33
	Seroprotection rate ¹	100% [89.4; 100]
Seroconversion rate ²	100% [89.4; 100]	100% [89.4; 100]
Seroconversion factor ³	52.97 [42.08;66.68]	389.64 [324.25;468.21]

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.

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

At days 21 and 42 and at month 6, the neutralising antibody responses were 57.1%, 96.4% and 86.4%, respectively, for the children aged 6 to 11 months; for the children aged 12 to 23 months, these were 57.1%, 100% and 92.3, respectively. For the children aged 24 to 35 months, these were 58.8% at day 21 and 100% at day 42 and month 6.

Immune response to Pandemrix H5N1

Two clinical studies have evaluated the immunogenicity of the monovalent pandemic influenza A vaccine (H5N1).

A dose finding study tested different haemagglutinin dosages of the vaccine in a vaccine volume of 1 ml, which is twice the vaccine volume of the final formulation. In this study, approximately 200 unprimed subjects aged 18-60 years received the adjuvanted vaccine following a 0, 21 days schedule. Fifty out of these 200 subjects received 3.75 μg HA/AS03, which is the haemagglutinin dosage of the final formulation.

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In a consistency study, more than 900 unprimed subjects aged 18-60 years received 3.75 µg HA/AS03 per 0.5 ml, which is the final formulation of the vaccine following a 0, 21 days schedule.

Immune response against vaccine strain:

Twenty-one days after the first and second dose of the vaccine, the seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody in the subjects who had received the final formulation of the vaccine were as follows:

anti-HA antibody	21 days after 1 st dose	21 days after 2 nd dose
Seroprotection rate*†	44.5%	94.3%
Seroconversion rate†	42.5%	93.7%
Seroconversion factor†	4.1	39.8

* anti-HA ≥1:40

† seroprotection rate (i.e. proportion of subjects with HI titre ≥ 1:40); seroconversion rate (i.e. 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); seroconversion factor (i.e; ratio of the post-vaccination GMT and the pre-vaccination GMT)

Twenty-one days after administration of the second dose, 96.0% of subjects had a 4-fold increase in serum neutralising antibody titres.

Persistence of immunogenicity:

In the dose finding study, persistence of immunogenicity up to 6 months after the second dose was evaluated in the 50 subjects who have received the 3.75 µg HA/AS03 formulation. The seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody at day 180 were respectively 54.0%, 52.0% and 4.4. A 4-fold increase in serum neutralising antibody titers at this time point was observed in 72% of subjects.

Cross-reactivity:

In both studies, the candidate vaccine showed the ability to induce a cross-reactive immune response against variants of the vaccine strain.

In the dose finding study, the seroprotection rate, seroconversion rate and seroconversion factor against H5N1 drift variants 21 days after the second dose in a subset of subjects were as follows:

anti-HA antibody	A/Indonesia/5/2005 N = 50	A/Anhui/01/2005 N = 20	A/Turkey/Turkey/1/2005 N = 20
Seroprotection rate*†	20.0%	35.0%	60.0%

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Seroconversion rate†	20.0%	35.0%	60.0%
Seroconversion factor†	2.0	3.4	4.7

* anti-HA \geq 1:40

† seroprotection rate (i.e. proportion of subjects with HI titre \geq 1:40); seroconversion rate (i.e. 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); seroconversion factor (i.e; ratio of the post-vaccination GMT and the pre-vaccination GMT)

Twenty one days after the second dose, a 4-fold increase in serum neutralising antibody titers was obtained in 77.1% of subjects against the A/Indonesia/5/2005 strain, in 75.0% of subjects against A/Anhui/01/2005 and in 85.0% of subjects against A/Turkey/Turkey/1/2005.

The consistency study confirmed that the candidate vaccine induces a cross-reactive immune response against A/Indonesia/5/2005. Twenty-one days after the second dose, seroconversion and seroprotection rates against this strain variant were both 50.2% with a seroconversion factor of 4.9. A 4-fold increase in serum neutralising antibody titers was obtained in 91.4% of subjects.

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 immunised 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 μ g HA were tested in the homologous challenge experiment, and doses of 15, 7.5, 3.8 or 1.75 μ g HA were tested in the heterologous challenge experiment. Control groups included ferrets immunised with adjuvant alone, non-adjuvanted vaccine (15 μ g HA) or phosphate buffered saline solution. Ferrets were vaccinated on days 0 and 21 and challenged intratracheally 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.

INDICATIONS

PANDEMRIX H1N1 is indicated for prophylaxis of influenza in an officially declared pandemic situation. *PANDEMRIX* should be used in accordance with official recommendations.

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CONTRAINDICATIONS

History of an anaphylactic reaction (i.e. life-threatening) to any of the constituents or trace residues of this vaccine. (Also see Precautions section).

PRECAUTIONS

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 and to residues.

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.

If the pandemic situation allows, immunisation should be postponed in patients with severe febrile illness or acute infection. Health care providers need to assess the benefits and potential risks of administering the vaccine to those patients.

PANDEMRIX should under no circumstances be administered intravascularly or intradermally. 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 bleeding.

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

A protective immune response may not be elicited in all vaccinees.

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

There are limited data available from *PANDEMRIX H1N1* in adults aged over 60 years and very limited data with *PANDEMRIX H1N1* or with a version of the vaccine containing H1N1 antigen in adults aged over 80 years.

There are no safety and immunogenicity data available from clinical studies with *PANDEMRIX H1N1* 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 ADVERSE REACTIONS). In particular rates of fever (axillary temperature $\geq 38^{\circ}\text{C}$) increased considerably after the second dose. Therefore, monitoring of temperature is recommended in young children post vaccination.

Epidemiological studies relating to Pandemrix in some EU countries have indicated a six- to 13-fold increased risk of narcolepsy with or without cataplexy in vaccinated as compared with

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unvaccinated children/adolescents. This risk increase has not been found in adults older than 20 years.

There are no safety, immunogenicity or efficacy data to support interchangeability of *PANDEMRIX H1N1* with other H1N1 pandemic vaccines.

Effects on Fertility:

There were no effects on the mating performance or fertility of female rats in a reproductive and developmental toxicity study in which rats were intramuscularly injected with Pandemrix H5N1 30 days prior to mating and on gestation days 6, 8, 11 and 15 (see also Use in Pregnancy).

Carcinogenicity:

No carcinogenicity studies have been conducted with *PANDEMRIX* or AS03 adjuvant.

Genotoxicity:

In standard genotoxicity tests, AS03 adjuvant was not mutagenic in *Salmonella typhimurium*, *E. coli* WP2uvrA or mouse lymphoma L5178Y cells *in vitro*, nor did it induce micronuclei in rat bone marrow erythrocytes *in vivo*.

Use in Pregnancy (Category B2):

No data have been generated in pregnant women with *PANDEMRIX* and with the AS03 adjuvant contained in the vaccine. Data from vaccinations with intrapandemic trivalent vaccines in pregnant women do not indicate that adverse foetal and maternal outcomes were attributable to the vaccine.

In a reproductive and developmental toxicity study in female rats intramuscularly injected with Pandemrix H5N1 (6µg H5 antigen and 0.1mL AS03 adjuvant), 30 days prior to mating and on gestation days 6, 8, 11 and 15, there were no significant toxicological effects on the dams, or their foetuses or pups. Anti-H5 antibodies were detected in all vaccine-treated females and their foetuses and pups.

Healthcare providers need to assess the benefits and potential risks of administering the vaccine to pregnant women.

Use in Lactation:

No data have been generated in breast-feeding women.

In a reproductive and developmental toxicity study with Pandemrix H5N1 in female rats, maternal treatment prior to mating and during gestation had no effect on pup development, assessed to lactation day 25. There was evidence of maternal antibodies to pup (see also Use in Pregnancy).

INTERACTIONS WITH OTHER MEDICINES

No data are available on the concomitant administration of *PANDEMRIX* with other vaccines.

Therefore, co-administration of *PANDEMRIX* is not recommended

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However, if co-administration with another vaccine is deemed necessary following benefit/risk assessment, immunisation should be carried out on separate limbs. In such cases, it should be noted that the adverse reactions may be intensified.

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

False positive ELISA serologic tests for HIV-1, Hepatitis C, and especially HTLV-1 may occur following influenza vaccination. These transient false-positive results may be due to cross-reactive IgM elicited by the vaccine. For this reason, a definitive diagnosis of HIV-1, Hepatitis C, or HTLV-1 infection requires a positive result from a virus-specific confirmatory test (e.g. Western Blot or immunoblot).

ADVERSE REACTIONS

Clinical Trial Experience

Adults aged 18 years and above

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

Adverse reactions reported are listed 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 $< 1/10,000$

Not known (cannot be estimated from the available data)

Blood and lymphatic system disorders

Uncommon: lymphadenopathy

Psychiatric disorders

Uncommon: insomnia

Nervous system disorders

Very common: headache

Uncommon: dizziness, paraesthesia

Gastrointestinal disorders

Common: gastro-intestinal symptoms (such as nausea, diarrhoea, vomiting, abdominal pain)

Skin and subcutaneous tissue disorders

Very common: sweating increased

Uncommon: pruritus rash

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Musculoskeletal and connective tissue disorders

Very common: myalgia, arthralgia

General disorders and administration site conditions

Very common: pain and swelling at the injection site, fatigue, shivering

Common: redness, pruritus at the injection site, fever

Uncommon: induration and warmth at the injection site, influenza like illness, malaise

The solicited local and general adverse events reported within 7 days of vaccination with Pandemrix H1N1, in the studies, D-Pan H1N1-007 and D-Pan H1N1-008 are provided below.

D-Pan-H1N1-007

This clinical study evaluated the reactogenicity of the first dose of Pandemrix H1N1 in healthy subjects aged 18-60 years. A concurrent group of subjects received the vaccine without AS03 adjuvant.

D-Pan-H1N1-007 (Day 0 to Day 6 solicited adverse events following 1 dose of 3.75 µg HA+ AS03 vaccine versus 1 dose of 15 µg HA unadjuvanted H1N1 vaccine) - Adverse Events with a causal relationship

Symptom	H1N1+AS03	H1N1
	N=63	N=65
Pain at the injection site	90.5%	35.4%
Redness at the injection site	1.6%	0.0%
Swelling at the injection site	7.9%	0.0%
Fatigue	33.3%	24.6%
Headache	23.8%	12.3%
Arthralgia	11.1%	4.6%
Myalgia	31.7%	6.2%
Shivering	9.5%	3.1%
Sweating	9.5%	7.7%
Fever ≥38°C	0.0%	0.0%
Fever ≥39°C	0.0%	0.0%

H1N1+ AS03 = H1N1 containing antigen-sparing dose of HA+AS03 adjuvant

H1N1 = H1N1 containing HA antigen without adjuvant

D-Pan-H1N1-008 – post dose 1

This clinical study evaluated the reactogenicity of the first dose Pandemrix H1N1 in healthy adults aged 18-60 and above 60 years.

D-Pan H1N1-008 (Day 0 to Day 6 solicited adverse events following a single dose of 3.75 µg HA + AS03 vaccine) - Adverse Events with a causal relationship

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Symptom	18-60 years	>60 years
	N=120	N=120
Pain at the injection site	87.5%	65.0%
Redness at the injection site	0.8%	7.5%
Swelling at the injection site	9.2%	10.0%
Fatigue	33.3%	20.0%
Headache	35.8%	17.5%
Arthralgia	14.2%	11.7%
Myalgia	20.8%	19.2%
Shivering	18.3%	5.8%
Sweating	14.2%	5.0%
Fever $\geq 38^{\circ}\text{C}$	0.8%	0.0%
Fever $\geq 39^{\circ}\text{C}$	0.0%	0.0%

Children aged 10-17 years

A clinical study evaluated the reactogenicity in children 10 to 17 years of age who received two doses of 0.5 ml (full dose) of Pandemrix H1N1 21 days apart. The per-dose frequency of the following adverse reactions was as follows:

Adverse reactions	Post dose 1	Post dose 2
	N=98	N=93
Pain at the injection site	92.9%	96.8%
Redness at the injection site	21.4%	28.0%
Swelling at the injection site	41.8%	53.8%
Shivering	14.3%	26.9%
Sweating	5.1%	7.5%
Fever $>38^{\circ}\text{C}$	3.1%	9.7%
Fever $>39^{\circ}\text{C}$	0.0%	1.1%
Arthralgia	26.5%	34.4%
Myalgia	34.7%	47.3%
Fatigue	40.8%	51.6%
Gastrointestinal	6.1%	6.5%
Headache	41.8%	53.8%

Children aged 3-9 years

A clinical study evaluated the reactogenicity in children 3 to 5 and 6 to 9 years of age who received a two doses of 0.25 mL (half the adult dose) of Pandemrix H1N1 21 days apart. The per-dose frequency of the following adverse reactions was as follows:

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Adverse reactions	3-5 years		6-9 years	
	Post dose 1	Post dose 2	Post dose 1	Post dose 2
	N=60	N=56	N=65	N=63
Pain at injection site	60.0%	55.4%	63.1%	65.1%
Redness at injection site	26.7%	41.1%	23.1%	33.3%
Swelling at injection site	21.7%	28.6%	23.1%	25.4%
Shivering	13.3%	7.1%	10.8%	6.3%
Sweating	10.0%	5.4%	6.2%	7.9%
Fever >38°C	10.0%	14.3%	4.6%	6.4%
Fever >39°C	1.7%	5.4%	0.0%	3.2%
Diarrhoea	5.0%	5.4%	NA	NA
Drowsiness	23.3%	17.9%	NA	NA
Irritability	20.0%	26.8%	NA	NA
Loss of appetite	20.0%	17.9%	NA	NA
Arthralgia	NA	NA	15.4%	14.3%
Myalgia	NA	NA	16.9%	17.5%
Fatigue	NA	NA	27.7%	20.6%
Gastrointestinal	NA	NA	13.8%	7.9%
Headache	NA	NA	21.5%	20.6%

Children aged 6-35 months

A clinical study evaluated the reactogenicity in children aged 6 to 35 months who received two doses of 0.25 ml following a 0, 21 days schedule. Axillary fever ($\geq 38^{\circ}\text{C}$), drowsiness and loss of appetite increased significantly after the second dose. The per-dose frequency of the following adverse reactions was as shown in the table:

Adverse reactions	Post dose 1	Post dose 2
	N=104	N=104
Pain	35.6%	41.3%
Redness	18.3%	32.7%
Swelling	11.5%	28.8%
Fever (>38°C) axillary	6.8%	41.4%
Fever (>39°C) axillary	1.0%	2.9%
Drowsiness	16.3%	33.7%
Irritability	26.9%	43.3%
Loss of appetite	17.3%	39.4%

The following adverse events have also been reported during post-marketing experience with *PANDEMRIX H1N1v*:

Immune system disorders: Anaphylaxis.

Nervous system disorders: Febrile convulsions, somnolence

Skin and subcutaneous tissue disorders: Angioedema, urticaria.

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General disorders and administration site conditions: Injection site reactions (such as inflammation, mass)

From Post-marketing surveillance with interpandemic trivalent vaccines, the following adverse events have been reported:

Blood and lymphatic system disorders: Transient thrombocytopenia.

Immune system disorders: Allergic reactions, in rare cases leading to shock.

Nervous system disorders: Neuralgia, convulsions. Neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome.

Vascular disorders: Vasculitis with transient renal involvement.

Skin and subcutaneous tissue disorders: Generalised skin reactions including urticaria

DOSAGE AND ADMINISTRATION

Dosage

Individuals aged 20 years and older:

One or two doses of 0.5 ml.

Immunogenicity data obtained at three weeks after administration of *PANDEMRIX H1N1* in clinical studies suggest 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.

Vaccination should be carried out by intramuscular injection.

Method of Administration

PANDEMRIX H1N1 consists of two containers: one multidose vial containing the antigen (suspension) and a second multidose vial containing the adjuvant (emulsion). The suspension is a colourless light opalescent liquid. The emulsion is a whitish to yellowish (milky) homogeneous liquid.

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 allowed to reach room temperature; 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 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. The vial containing the adjuvant

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should be maintained in an upside down position to facilitate the withdrawal of the full contents.

3. After the addition of the adjuvant to the antigen, the mixture should be well shaken. The mixed vaccine is a whitish to yellowish (milky) homogenous emulsion. In the event of other variation being observed, discard the vaccine.
4. The volume of *PANDEMRIX H1N1* vial after mixing is at least 5 mL. The vaccine should be administered in accordance with the recommended posology (see Dosage and Administration).
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 allowed to reach room temperature before each withdrawal.

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

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

OVERDOSAGE

Insufficient data are available.

For advice on management of over dosage, please contact the Poisons Information Centre on 131126

PRESENTATION AND STORAGE CONDITIONS

Presentations

2.5 ml suspension in a vial (type I glass) for 10 doses with a stopper. Pack size of 50.

2.5 ml emulsion in a vial (type I glass) for 10 doses with a stopper. Pack size of 25 X 2.

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Storage

PANDEMRIX H1N1 must be stored in a refrigerator between +2°C and +8°C and be protected from light. DO NOT FREEZE.

The expiry date of the vaccine is indicated on the label and packaging. The shelf life of *PANDEMRIX H1N1* is 3 years from the date of manufacture if stored between temperatures of +2°C and +8°C.

After mixing, the vaccine should be used within one working day.

MANUFACTURER:

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NAME AND ADDRESS OF THE SPONSOR:

GlaxoSmithKline Australia Pty Ltd,
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Abbotsford, Victoria, 3067

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription only medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 9 August 2010

Date of most recent amendment: 4 July 2012

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