Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Influenza virus haemagglutinin (Type A/California/7/2009 (H1N1)v-like strain adjuvanted to ASO3)

Proprietary Product Name: Pandemrix H1N1 pandemic influenza vaccine

Sponsor: GlaxoSmithKline Australia Pty Ltd

February 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Copyright
© Commonwealth of Australia 2013
This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <tga.copyright@tga.gov.au>.

Contents

I. Introduction to product submission

Submission details

Type of Submission	Major variation: Change in patient group and dosing schedule.
Decision:	Not approved: Proposed amendment to include dosage instructions for children aged 6 months to 17 years in the Product Information. Approved: Other revisions to the Product Information, including amendment of the *Dosage* section to state: "*Individuals aged 20 years and older: One or two doses of 0.5ml*"; and inclusion, under the *Clinical Trials* and *Adverse Reactions* sections, of data from clinical trials in those aged 6 months to 17 years.
Date of Decision:	4 July 2012
Active ingredient:	Influenza virus haemagglutinin (A/California/7/2009(H1N1)v-like strain)
Product Name:	Pandemrix H1N1 pandemic influenza vaccine split virion inactivated AS03 adjuvanted 0.5 mL dose
Sponsor's Name and Address:	GlaxoSmithKline Australia Pty Ltd. PO Box 168 Boronia, Victoria 3155, Australia
Dose form:	Injection suspension
Strength:	The product is presented in two vials: one containing 2.5 mL suspension (antigen), for 10 doses, and the other containing 2.5 mL emulsion (adjuvant), for 10 doses. The two components are mixed prior to administration. One reconstituted single dose is 0.5 mL, containing 3.75 µg haemagglutinin antigen from A/California/7/2009(H1N1)v-like strain.
Container:	Glass vial
Pack size:	50 composite packs (of two vials) per carton
Approved Therapeutic use:	*Pandemrix H1N1 is indicated for prophylaxis of influenza in an officially declared pandemic situation. PANDEMRIX H1N1 should be used in accordance with official recommendations.*
Route(s) of administration:	Intramuscular (IM) injection
Dosage:	See below.
ARTG Number:	174554

Product background

Pandemrix H1N1 pandemic influenza vaccine is an inactivated, split virion monovalent vaccine containing A/California/7/2009(H1N1)v-like strain. The vaccine is adjuvanted with the proprietary Ajuvant System 03 (ASO3). The ASO3 is composed of squalene, DL–α–tocopherol and polysorbate 80.

This vaccine is not intended for use in routine prophylaxis of seasonal influenza but is meant to act as a template for manufacture of an influenza vaccine with an updated strain in the event of a pandemic. In 2008, Pandemrix was first registered as a H5N1 pandemic mock up vaccine in Australia. Following the 2009 H1N1 influenza pandemic, Pandemrix H5N1 was updated to Pandemrix H1N1 vaccine. In 2010, Pandemrix H1N1was registered in Australia based on immunogenicity data.

The indication for Pandemrix approved by TGA is as follows:

> *Pandemrix H1N1 is indicated for prophylaxis of influenza in an officially declared pandemic situation. Pandemrix should be used in accordance with the official recommendation.*

No changes are proposed for the currently approved therapeutic indication.

Proposed amendments

The current application seeks to amend the *Dosage and Administration*, *Clinical Trials*, and *Adverse Reactions* sections of the Pandemrix Product Information (PI) to include findings from 3 clinical trials of Pandemrix in children aged 6 months to 17 years. Pandemrix is currently indicated in adults aged 18 years or over. Changes proposed in this application under the *Dosage* subsection of the PI aim include use in children aged 6 months to 17 years.

The currently approved *Dosage* subsection of the PI is as follows:

> *Adults aged 18 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.*

The sponsor proposes to include the following under this section:

- *Children and adolescents aged 10-17 years*

  Dosing may be in accordance with the recommendations for adults.

- *Children aged 6 months to 9 years*

  One dose of 0.25mL at an elected date

  There is a further immune response to a second dose of 0.25mL administered after an interval of 3 weeks.

- *Children aged less than 6 months*

  Vaccination is not currently recommended in this age group.

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

Specific details of other changes proposed to the PI in relation to the use of Pandemrix in children are beyond the scope of this AusPAR.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 26 August 2010. As of April 2012, Pandemrix is registered in about 11 countries, including the following (Table 1):

Table 1. Pandemrix international regulatory status.

indications		
Countries: Europe, Iceland, Norway *Submission date:* 30 July 2009 *Approval date:* 29 September 2009 *Expiry date:* 29 September 2014	Prophylaxis of influenza caused by A (H1N1)v 2009 virus. In persons under 20 years of age, Pandemrix should only be used if the recommended annual seasonal trivalent influenza vaccine is not available and if immunisation against (H1N1)v is considered necessary. Pandemrix should be used in accordance with Official Guidance.	*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. *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.* Vaccination is not currently recommended in this age group. It is recommended that subjects who receive a first dose of Pandemrix should complete the vaccination course with Pandemrix.
Country: Switzerland *Submission date:* 30 July 2009 *Approval date:* 23 February 2009 *Expiry date:* 22 October 2014	For the prophylaxis of influenza caused by A/California/7/2009 in children aged 6months to 17years, young adults aged 18-60 years, and elderly adults aged over 60 years of age in the event of an officially declared pandemic.	*Children aged 3 to 17 years:* One 0.5 mL dose at an elected date. The available data indicate that a single administration of a 0.5ml dose (equivalent to an adult dose) results in a sufficient immune response (see "Properties/Effects"). A second dose is not recommended in immunecompetent children from 3 to 17

Details	Approved indications	Posology in paediatric patients
	Pandemrix is to be used in conformity with the official recommendations issued by the Federal Office of Public Health (see "Posology and method of administration" and "Properties/Effects").	years. *Children aged 6 to 35 months:* One 0.25 mL dose (half the adult dose) at an elected date. The available data indicate that a single administration of a 0.25 mL dose (equivalent to half an adult dose) results in a sufficient immune response (see "Properties / Effects"). A second dose is not recommended in children (see "Warnings and Precautions"). *Infants under 6 months of age:* Vaccination is currently not recommended in this age group.
World Health Organization Submission date: 2 December 2009 *Approval date:* 21 December 2009 *Expiry date:* 21 December 2014	Aligned on the European Union (EU) Summary of Product Characteristics (SmPC).	Aligned on the EU SmPC

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

Introduction

This application consisted of clinical data only, comprising 3 clinical studies: D-Pan-H1N1-009, D-Pan-H1N1-010 and D-Pan-H1N1-023 (Studies 009, 010 and 023, respectively). Study 009 was carried out in children 6-35 months, whereas Studies 010 and 023 were prime-boost studies in children 3-17 years of age, conducted with a full adult dose (3.75 –μg haemagglutinin antigen; HA) and half the adult dose (1.9 μg HA).

This is an antigen sparing vaccine with 0.5 mL of vaccine (adult dose) containing 3.75 μg of HA adjuvanted with ASO3. The presentation is multidose vials of antigen and adjuvant separately which are mixed at the time of administration.

The vaccine virus is grown in chicken eggs. The monovalent vaccine product contains inactivated, split virion adjuvanted with the proprietary ASO3 system. The ASO3 adjuvant system is composed of squalene, DL-α-tocopherol and polysorbate 80.

This vaccine is not intended for use in routine prophylaxis of seasonal influenza but is meant to act as a template for manufacture of an influenza vaccine with an updated strain in the event of a pandemic. Beginning with the A/H5N1 template, the product was updated to A/H1N1 during the 2009-10 pandemic and was used extensively in Europe but not in Australia.

Registration is based on immunogenicity outcomes. The immune response to vaccine is assessed with reference to the Committee for Medicinal Products for Human Use (CHMP) criteria for immunogenicity of seasonal trivalent influenza vaccine in adults in the 18–60 year age group. These criteria for homologous antibodies against HA using a haemagglutination inhibition (HI) assay include:

1. Seroconversion Rate (SCR) > 40%;
2. Seroconversion Factor (SCF) > 2.5 fold, and
3. Seroprotection Rate (SPR; ≥ 1/40) > 70%.

For mock-up pandemic influenza vaccines, all three must be met.

Good clinical practice aspects

The studies included in the dossier are stated to have complied with the principles of Good Clinical Practice and the applicable ethical standards.

Pharmacokinetics

Not applicable.

Pharmacodynamics

Not applicable.

Efficacy

Study 009

This was a study of the immunogenicity of Pandemrix H1N1 pandemic influenza vaccine (A/California/7/2009 (H1N1)v-like antigen) in children aged 6 months to 35 months. This multicentre study was conducted in Spain in 2009-10.

Study design

The trial design was (in part) randomised and open-labelled, with healthy children aged 6 to 35 months allocated to 2 parallel vaccine groups. The 2 vaccine groups were 3.75 μg HA/AS03$_A$ and 1.9 μg HA/AS03$_B$, with randomisation in a ratio of 2:1, respectively.

There were a total of 157 participants in the Total Vaccinated Cohort (TVC), stratified to the following 3 age strata:

- 6-11 months (n = 51)
- 12-23 months (n = 54)
- 24-35 months (n = 52)

The enrolment was done sequentially as follows:

Step 1: Enrolment of 53 subjects into vaccine group 1.9 μg HA/AS03$_B$. After satisfactory review of reactogenicity on Day 7, enrolment proceeded to Step 2.

Step 2: Randomised (1:1) allocation of 104 subjects to both vaccine groups, that is, 1.9 μg HA/AS03$_B$ and 3.75 μg HA/AS03$_A$.

The resulting total of 157 participants was distributed as follows:

Group A: 53 subjects (16, 20 and 17 subjects in 6-11, 12-23 and 24-35 months age strata respectively). This group received the 'full dose' (3.75 μg HA/AS03$_A$ vaccine).

Group B: 104 subjects (35, 34 and 35 subjects in 6-11, 12-23 and 24-35 months age strata respectively). This group received the 'half dose' (1.9 μg HA/AS03$_B$ vaccine).

Note that the suffixes A or B with the ASO3 indicate vaccine dose group (adult/full dose or baby/half dose).

The ASO3$_A$ was withdrawn from the unique ASO3 vial and administered as a 'full dose' of 250 μL of oil-in-water emulsion in an overall injection volume of 0.5 mL reconstituted vaccine containing 3.75 μg HA (Group A).

The ASO3$_B$ was withdrawn from the unique ASO3 vial and administered as a 'half dose' of 125 μL of oil-in-water emulsion in an overall injection volume of 0.25 mL reconstituted vaccine containing 1.9 μg HA (Group B).

The two doses were administration by the intramuscular (IM) route, 3 weeks apart on Days 0 and 21. The report includes primary immunogenicity results up to the Day 42 after Dose 1; that is, 21 days after Dose 2.

Objectives

The primary objective was to evaluate homologous HI immune response with respect to the CHMP criteria, using adult correlates, at 21 days after Dose 2.

There were a number of secondary objectives including the following:

1. Assessment of immunogenicity of 2 doses of Pandemrix H1N1 vaccine containing 1.9 μg HA/AS03B, in terms of homologous anti-HA antibody response, at 21 days after each vaccine dose and at Month 11-12.
2. Assessment of immunogenicity of 2 doses of Pandemrix H1N1 vaccine containing 3.75 μg HA/AS03A, in terms of homologous anti-HA antibody response, at 21 days after each vaccine dose and at Month 11-12.
3. Assessment of the neutralising antibodies response at each timepoint in a subset of participants.

The primary immunogenicity analysis was carried out on the According-to-Protocol (ATP) cohort for immunogenicity overall (n = 151) and for each age stratum.

The overall mean age was 19.5 ± 9.15 months in the ATP cohort for immunogenicity wherein 44.4% subjects were female and mainly (90%) of Caucasian ethnicity.

The overall mean ages were 9.1 ± 1.33 months, 18.4 ± 3.01 months and 30.5 ± 3.39 months in 6-11, 12-23 and 24-35 age strata respectively in Total Vaccinated Cohort (TVC).

Results

At Day 0, the overall seropositivity rate was 12.5% and 5.0% in Group A and Group B, respectively. The highest seropositivity rate at baseline (25%) was observed in the 24–35 month age stratum in Group A. The overall geometric mean titer (GMT) values at baseline were below the cut-off for seropositivity at 6.8 and 5.7 for Groups A and B respectively.

At 21 Days after the first dose, overall SPR as well as within each age strata was 100% in both Groups. The overall GMTs rose to 322.30 and 313.48 in Group A and Group B respectively at this timepoint. The overall SCR at this timepoint were 97.9% and 99.0% in Groups A and B respectively. The overall SCF were 46.29 fold and 54.47 fold in Group A and B respectively at this timepoint.

After 21 Days after second Dose (Day 42), the GMTs increased further in both groups and in all age strata with overall values at 2259.61 and 2007.70 in Group A and Group B respectively. The overall SPR and SCR were 100% in both groups. The SCF were 322.67 and 346.86 in Group A and B respectively. The overall (all age strata) results are provided in Table 2, below:

Table 2. Overall (all age strata) HI antibody response

H1N1 HI Antibodies against A/California/7/2009 (H1N1)																	
		≥10 1/DIL			GMT			SPR			SCR			SCF		
			95% CI			95% CI			95% CI			95% CI			95% CI	
Timing	N	%	LL	UL	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
Overall (3.75 µg/AS03$_A$)																
PRE	48	**12.5**	4.7	25.2	**6.82**	5.22	8.91	**8.3**	2.3	20.0						
PI(D21)	48	**100**	92.6	100	**322.30**	265.43	391.35	**100**	92.6	100	**97.9**	88.7	99.9	**46.29**	35.42	60.49
PII(D42)	50	**100**	92.9	100	**2259.61**	1947.61	2621.59	**100**	92.9	100	**100**	92.6	100	**322.67**	231.61	449.52
Overall (1.9 µg/AS03$_B$)																
PRE	101	**5.0**	1.6	11.2	**5.75**	5.00	6.63	**3.0**	0.6	8.4						
PI(D21)	101	**100**	96.4	100	**313.48**	270.89	362.77	**100**	96.4	100	**99.0**	94.6	100	**54.47**	46.39	63.96
PII(D42)	97	**100**	96.3	100	**2007.70**	1805.24	2232.87	**100**	96.3	100	**100**	96.3	100	**346.86**	287.54	418.42

N = number of subjects with available results; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; PRE = Pre-vaccination at Day 0; PI (D21) = Post-vaccination at Day 21; PII (D42) = Post-vaccination at Day 42; GMT = geometric mean antibody titre calculated on all subjects; SPR=Seroprotection rate: percentage of vaccinees with serum HI titre >= 40 1/DIL; SCR=Seroconversion Rate (Seroconversion defined as: For initially seronegative subjects, antibody titre >= 40 1/DIL after vaccination; For initially seropositive subjects, antibody titre after vaccination >= 4 fold the pre-vaccination antibody titre); SCF = Seroconversion Factor or geometric mean ratio (mean[log10(POST/PRE)])

The summary of age strata specific results is shown below (Table 3).

Table 3. HI antibody response according to age strata. Table continued across two pages.

Study 009				Estimate		
	Age strata (months)	Group	Timepoint		LL	UL
SPR (%)	6-11	B	D21	100	89.7	100
				D42	100	89.1
		A	D21	100	78.2	100
				D42	100	78.2
SPR (%)	12-23	B	D21	100	89.7	100
			D42	100	89.1	100
		A	D21	100	80.5	100
			D42	100	81.5	100

Study 009				Point Estimate	95% CI	
	Age strata (months)	Group	Timepoint		LL	UL
SPR (%)	24-35	B	D21	100	89.4	100
			D42	100	89.4	100
		A	D21	100	79.4	100
			D42	100	80.5	100
SCR (%)	6-11	B	D21	97.1	84.7	99.9
			D42	100	89.1	100
		A	D21	100	78.2	100
			D42	100	78.2	100
SCR (%)	12-23	B	D21	100	89.7	100
			D42	100	89.1	100
		A	D21	100	79.4	100
SCR (%)	6-11	B	D21	97.1	84.7	99.9
			D42	100	80.5	100
SCR (%)	24-35	B	D21	100	89.4	100
			D42	100	89.4	100
		A	D21	93.8	69.8	99.8
			D42	100	79.4	100
SCF (x)	6-11	B	D21	48.12	34.3	67.4
			D42	276.14	167	456
		A	D21	46.29	35.8	59.8
			D42	370.48	218	630

Study 009				Point Estimate	95% CI	
	Age strata (months)	Group	Timepoint		LL	UL
SCF (x)	12-23	B	D21	63.37	48.1	83.4
			D42	386.45	309	484
		A	D21	64.06	38.6	106
			D42	472.16	344	649
SCF (x)	24-35	B	D21	52.97	42.1	66.7
			D42	389.64	324	468
		A	D21	33.44	18.6	60.2
			D42	189.16	83.8	427

The results using TVC as well as the results stratified by pre-vaccination serostatus were provided in the dossier and were consistent with the overall analyses provided above based on ATP cohort analyses.

Evaluator's comment: Following only Dose 1 with half-dose vaccine, the immune response with respect to homologous anti-HA antibodies exceeded the CHMP criteria for immunogenicity of influenza vaccines using adult thresholds in all age strata. Dose 2 further augmented the immune response, the significance of which is not clear, as indeed is the relevance of adult immune criteria for use in children. Note the mean age in the 6-11 months age strata was 9 months.

The results for neutralising antibodies were not available in this dossier.

Study 010

This was a study of the immunogenicity of Pandemrix H1N1 pandemic influenza vaccine (A/California/7/2009(H1N1)v-like strain) in children aged 3 years to 17 years. This multicentre study was conducted in Spain in 2009.

Study design

The design of the study was non-randomised and open-label with healthy children aged 3–17 years who received 3 IM doses of Pandemrix H1N1 pandemic vaccine containing 3.75 µg HA/AS03$_A$ according to a Day 0, Day 21 (primary vaccination) and Month 6 (booster) schedule.

A total of 210 healthy children, stratified to 3 age strata, were enrolled in the study as follows:

- 3-5 years (n = 53)
- 6-9 years (n = 57)
- 10-17 years (n = 100)

Objectives

The two sequential co-primary serological endpoints were as follows:

1. Assessment of homologous anti-HA antibody immune response at 21 days post Dose 2 with respect to the CHMP criteria for immunogenicity of influenza vaccines in adults.
2. Assessment of homologous anti-HA antibody immune response after a booster dose of Pandemrix H1N1 pandemic vaccine administered at Month 6 after completion of 2 dose primary vaccination.

There were a number of secondary endpoints including the following:

1. Assessment of homologous anti-HA antibody immune response at 21 days after Dose 1 and at 6 months (pre-booster).
2. Assessment of homologous anti-HA antibody response at 7 days, 6 months and one year after the booster dose at Month 6.
3. Assessment of neutralising antibodies immune response at each timepoint in a subset of participants.

The report comprises primary immunogenicity results following completion of primary vaccination (Day 42). Note that only an abridged report was included in the dossier.

The overall mean age of the participants was 9.2 years in the TVC. The mean ages were 3.5 ± 0.7 years, 7.5 ± 1.18 years and 13.3 ± 2.23 years in 3-5, 6-9 and 10-17 years age strata, respectively. Overall 55% children were female and predominantly Caucasian (99%).

A total of 198 subjects were included in the ATP cohort for immunogenicity, with 51, 55 and 92 in the 3 age strata respectively.

Results

- At Day 0, the overall seropositivity rate across the 3 age strata was 20.2%. The age strata specific seropositivity rates at baseline were 0%, 12.7% and 35.9% in 3-5, 6-9 and 10-17 years age strata respectively.
- At 21 days after Dose 1, SPRs were 100% in all age strata. The SCR were 100%, 100% and 96.7% in 3-5, 6-9 and 10-17 years age strata respectively. The SCF were 49, 59 and 72 fold in the 3 groups respectively.
- At 42 days after Dose 1, SPRs were 100% in all age strata. The SCR were 100%, 100% and 96.6% in 3-5, 6-9 and 10-17 years age strata respectively. The SCF were 384, 225, and 139 fold in the 3 groups respectively.

Table 4 provides a summary of the results:

Table 4. Anti-HA antibodies against A/California/7/2009 (H1N1) (ATP cohort for immunogenicity)

		≥10 1/DIL			GMT			SPR			SCR			SCF		
			95% CI			95% CI			95% CI			95% CI			95% CI	
	N	%	LL	UL	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
Overall																
PRE	198	20.2	14.8	26.5	7.4	6.4	8.5	8.6	5.1	13.4	-	-	-	-	-	-
PI(D21	198	100	98.2	100	456.5	400.5	520.3	100	98.2	100	98.5	95.6	99.7	61.8	54.3	70.3
PI(D42	194	100	98.1	100	1538.5	1419.0	1668.0	100	98.1	100	98.5	95.5	99.7	208.5	179.0	242.9
3 to 5 years stratum																
PRE	51	0.0	0.0	7.0	5.0	5.0	5.0	0.0	0.0	7.0	-	-	-	-	-	-
PI(D21	51	100	93.0	100	245.4	209.3	287.8	100	93.0	100	100	93.0	100	49.1	41.9	57.6
PI(D42	51	100	93.0	100	1924.3	1681.9	2201.6	100	93.0	100	100	93.0	100	384.9	336.4	440.3
6 to 9 years stratum																
PRE	55	12.7	5.3	24.5	6.6	5.3	8.1	7.3	2.0	17.6	-	-	-	-	-	-
PI(D21	55	100	93.5	100	386.5	301.9	494.9	100	93.5	100	100	93.5	100	59.0	48.3	72.0
PI(D42	55	100	93.5	100	1479.6	1296.5	1688.5	100	93.5	100	100	93.5	100	225.7	182.7	278.2
10 to 17 years stratum																
PRE	92	35.9	26.1	46.5	9.8	7.6	12.7	14.1	7.7	23.0	-	-	-	-	-	-
PI(D21	92	100	96.1	100	711.1	592.0	854.2	100	96.1	100	96.7	90.8	99.3	72.2	57.2	91.2
PI(D42	88	100	95.9	100	1384.9	1210.7	1584.1	100	95.9	100	96.6	90.4	99.3	139.1	105.7	183.1

SPR = percentage with antibody titer ≥40; SCR = percentage with antibody titer ≥ 40 1/DIL after vaccination for initially seronegative subjects, or ≥4 fold the pre-vaccination antibody titer for initially seropositive subjects; SCF = fold increase in GMTs post-vaccination compared with pre-vaccination; PRE = pre-vaccination; PI(D21) = post-vaccination at Day 21; PI(D42) = post-vaccination at Day 42; LL = Lower Limit; UL = Upper Limit; N = number of subjects with available results

The immunogenicity results stratified by baseline serostatus indicate robust immune response regardless of baseline serostatus.

Evaluator's comment: Adequate homologous HI immune response in all age strata (3-17 years) was achieved following single adult dose of vaccine with respect to the CHMP criteria using adult thresholds.

The Day 42 showed further accentuation of immune response following administration of Dose 2. In view of satisfactory immune response to Dose 1, the clinical need and significance of a second dose is uncertain.

The results for neutralising antibodies and booster dose were not available in this dossier. The sponsor is proposing half-dose vaccine up to 9 years of age based on the following study (023).

Study 023

This was study of immunogenicity of Pandemrix H1N1 pandemic influenza vaccine (A/California/7/2009(H1N1)v-like strain) in children aged 3 years to 17 years. This multicentre study was conducted in Germany in 2009.

Design

The design of the study was non-randomised and open-label with healthy children aged 3–17 years who received 3 IM doses of Pandemrix H1N1 pandemic vaccine containing 1.9 μg HA/AS03$_B$ according to Day 0, Day 21 (primary vaccination) and Month 6 (booster) schedule.

A total of 245 healthy children, stratified by age with allocation in a ratio of 1:1:2 respectively were as follows:

- 3-5 years (n = 61)
- 6-9 years (n = 65)
- 10-17 years (n = 118)

The subjects were also randomised (1:1) to one of the two blood sampling (BS) schedules (BS1 and BS2). The blood samples were collected on Days 0, 21, 42 and Month 6 in BS1 and were collected on Day 42, Month 6, Month 6/7 and Month 12 in BS2.

Objectives

The primary objective of the study was to evaluate homologous antibody immune response at 21 days after 2 doses (Day 42) of Pandemrix pandemic vaccine with respect to CHMP criteria for immunogenicity of influenza vaccines in adults.

The secondary objectives included the following:

1. Assessment of homologous anti-HA antibody immune response at 21 days after Dose 1 and at 6 months.
2. Assessment of homologous anti-HA antibody response at 7 days and 6 months after the booster dose given at Month 6.
3. Assessment of neutralising antibodies immune response at each timepoint in a subset of participants.

The report comprises primary immunogenicity results following completion of post primary vaccination (Day 42). Note that only an abridged report was included in the dossier.

Results

A total of 225/245 (92%) subjects were included in the ATP cohort for immunogenicity, with 54, 60 and 111 in the 3 age strata, respectively.

The overall mean age of the participants was 9.3 years in the ATP cohort for immunogenicity. The mean ages were 4.1 ± 0.85 years, 7.3 ± 1.13 years and 12.9 ± 2.19 years in the 3-5, 6-9 and 10-17 years age strata, respectively. Overall 46.7% children were female and predominantly Caucasian (96%).

At the time of reporting, the results are available for all timepoints in BS1 group (Days 0, 21 and 42) and for BS2 group at Day 42.

- At Day 0, the overall pre-vaccination seropositivity rate (≥ 1/10 dilution) for the subjects in BS1 group was 17.9% (7.1%, 3.3% and 31.5% in 3-5, 6-9 and 10-17 years strata, respectively). The seropositivity rate for BS2 at Day 42 was 100%, overall and in each age strata.

- The pre-vaccination GMT value in BS1 group was 7.3 (5.7, 5.2 and 9.9 in 3-5, 6-9 and 10-17 years age strata respectively).
- At Day 21 after Dose of vaccine, the overall GMT value rose to 297.9 (192.6, 190.3 and 479.3 in 3-5, 6-9 and 10-17 years age strata respectively) in BS1 group.
- At Day 42, that is, 21 days after Dose 2 of vaccine, further increase in overall GMT value (1106.7) was observed (1361.7, 970.1 and 1069.4 in 3-5, 6-9 and 10-17 years age strata respectively) in BS1 group.
- At Day 42, the GMT value in BS2 group was 999.4 overall (1161.7, 915.7 and 979.6 in the 3 age strata respectively).

The results are summarised in Table 5:

Table 5. Summary of immunogenicity results.

		≥10 1/DIL			GMT			SPR			SCR			GMFR		
			95% CI			95% CI			95% CI			95% CI			95% CI	
Timing	N	%	LL	UL	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
BS1: Overall																
PRE	112	17.9	11.3	26.2	7.3	6.1	8.8	6.3	2.5	12.5	-	-	-	-	-	-
PI(D21)	112	100	96.8	100	297.9	247.8	358.3	99.1	95.1	100	98.2	93.7	99.8	40.87	34.41	48.55
PII(D42)	112	100	96.8	100	1106.7	983.2	1245.8	100	96.8	100	99.1	95.1	100	151.82	124.27	185.48
BS1: 3-5 years stratum																
PRE	28	7.1	0.9	23.5	5.7	4.5	7.2	3.6	0.1	18.3	-	-	-	-	-	-
PI(D21)	28	100	87.7	100	192.6	145.6	254.8	100	87.7	100	100	87.7	100	33.62	26.25	43.05
PII(D42)	28	100	87.7	100	1361.7	1107.0	1674.9	100	87.7	100	100	87.7	100	237.68	175.28	322.29
BS1: 6-9 years stratum																
PRE	30	3.3	0.1	17.2	5.2	4.8	5.8	0.0	0.0	11.6	-	-	-	-	-	-
PI(D21)	30	100	88.4	100	190.3	147.0	246.3	100	88.4	100	100	88.4	100	36.33	27.96	47.22
PII(D42)	30	100	88.4	100	970.1	765.8	1228.8	100	88.4	100	100	88.4	100	185.25	142.09	241.52
BS1: 10-17 years stratum																
PRE	54	31.5	19.5	45.6	9.9	7.0	14.1	11.1	4.2	22.6	-	-	-	-	-	-
PI(D21)	54	100	93.4	100	479.3	361.8	634.9	98.1	90.1	100	96.3	87.3	99.5	48.29	35.64	65.42
PII(D42)	54	100	93.4	100	1069.4	892.6	1281.3	100	93.4	100	98.1	90.1	100	107.74	76.64	151.45
BS2: Overall																
PII(D42)	25	100	96.8	100	999.4	900.7	1108.8	100	96.8	100	-	-	-	-	-	-
BS2: 3-5 years stratum																
PII(D42)	30	100	86.3	100	1161.7	905.2	1490.9	100	86.3	100	-	-	-	-	-	-
BS2: 6-9 years stratum																
PII(D42)	57	100	88.4	100	915.7	759.1	1104.6	100	88.4	100	-	-	-	-	-	-
BS2: 10-17 years stratum																
PII(D42)	112	100	93.7	100	979.6	845.3	1135.2	100	93.7	100	-	-	-	-	-	-

GMT = Geometric Mean Titer; SPR = Seroprotection rate: percentage of subjects with antibody titer ≥ 1:40; SCR = Seroconversion rate: percentage of subjects with antibody titer ≥ 40 1/DIL after vaccination for initially seronegative subjects, or ≥4 fold the pre-vaccination antibody titer for initially seropositive subjects; GMFR = Geometric Mean Fold Rise: fold increase in GMTs post-vaccination compared with pre-vaccination; PRE = pre-vaccination; PI(D21) = post-vaccination I at Day 21; PII(D42) = post-vaccination II at Day 42; LL = Lower Limit; UL = Upper Limit; N = number of subjects with available results. BS1= Blood sampling group 1; BS2= Blood sampling group 2.

In BS1, the overall SPR was 6.3% pre-vaccination and 99.1% at Day 21 after Dose 1 (3.6% at Day 0 and 100% at Day 21 for the 3-5 years age group, 0% at Day 0 and 100% at Day 21 for the 6-9 years age group, and 11.1% at Day 0 and 98.1% at Day 21 for the 10-17 years age group). At Day 42, the observed value of SPR was 100% overall and in each age stratum in BS1 group.

The SPR observed for BS2 at Day 42 was 100% overall and in each age stratum.

The overall SCR in BS1 group at Day 21 and Day 42 were 98.2% and 99.1% respectively (100% at Days 21 and 42 for the 3-5 and the 6-9 years age group and 96.3% at Day 21 and 98.1% at Day 42 for the 10-17 years age group).

The overall Geometric Mean Fold Rise (GMFR) in BS1 group at was 40.87 at Day 21 and 151.82 at Day 42 (33.62 at Day 21 and 237.68 at Day 42 for the 3-5 years age group, 36.33 at Day 21 and 185.25 at Day 42 for the 6-9 years age group and 48.29 at Day 21 and 107.74 at Day 42 for the 10-17 years age group).

The immunogenicity results stratified by baseline serostatus were consistent with the overall analysis.

Evaluator's comment: This study examined homologous anti-HA immune response using 1.9 µg/ASO3 adjuvanted vaccine using prime-boost schedule and complements information from the preceding Study 010 which was conducted using full dose vaccine in the same age group.

All CHMP criteria were satisfactorily demonstrated using adult thresholds with single injection of half the adult dose.

The proposed vaccination using half dose (1.9 µg HA) in age group 6 months to 35 months is supported based on the results in the Study 009.

The proposed vaccination using half dose (1.9 µg HA) in the age group 3-9 years is supported based on the results in the Studies 009 and 023.

Study 023 also demonstrated that a single half dose (1.9 µg HA) was able to elicit adequate immune response in the 10-17 years age group as well, so that the proposed adult dosing (3.75 µg HA) in this age group is not supported.

Safety

Study 009

Primary safety analysis

The primary safety analysis was performed on the TVC. Overall, the incidence of any adverse event (AE) (solicited and unsolicited) by dose during the 7-day post vaccination period (Days 0 to 6) was 92.4% and 84.1% in Groups A and B respectively and was reported in 98.1% Group A subjects and 96.2 Group B subjects. The reporting frequency of any Grade 3 symptom in 7 days post Dose 1 was 26.7% versus 6.7% in Groups A and B respectively and was 45.3% versus 13.5% following Dose in the 2 respective groups. The incidences of solicited local symptoms following each dose in first 7 days were as follows (Table 6):

Table 6. Summary of adverse event findings by dose.

Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose											
		3.75 µg/AS03$_A$					1.9 µg/AS03$_B$				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Pain	All	53	31	**58.5**	44.1	71.9	104	37	**35.6**	26.4	45.6
	Grade 3	53	0	**0.0**	0.0	6.7	104	1	**1.0**	0.0	5.2
Redness (mm)	All	53	17	**32.1**	19.9	46.3	104	19	**18.3**	11.4	27.1
	[50.1 - ...	53	2	**3.8**	0.5	13.0	104	0	**0.0**	0.0	3.5
Swelling (mm)	All	53	11	**20.8**	10.8	34.1	104	12	**11.5**	6.1	19.3
	[50.1 - ...	53	1	**1.9**	0.0	10.1	104	0	**0.0**	0.0	3.5
Dose 2											
Pain	All	52	27	**51.9**	37.6	66.0	104	43	**41.3**	31.8	51.4
	Grade 3	52	2	**3.8**	0.5	13.2	104	3	**2.9**	0.6	8.2
Redness (mm)	All	52	23	**44.2**	30.5	58.7	104	34	**32.7**	23.8	42.6
	[50.1 - ...	52	6	**11.5**	4.4	23.4	104	1	**1.0**	0.0	5.2
Swelling (mm)	All	52	17	**32.7**	20.3	47.1	104	30	**28.8**	20.4	38.6
	[50.1 - ...	52	4	**7.7**	2.1	18.5	104	1	**1.0**	0.0	5.2

Pain, redness and swelling were the most frequently reported solicited local symptom after each dose in both Groups and showed dose effect, that is, higher frequency of occurrence in Group A (3.75 µg HA) compared to Group B (1.9 µg HA).

In addition, the reported frequencies of local symptoms during the 7 day post vaccination period indicated a trend towards increase in frequency of local reactions following the second dose.

Overall, 69.8% versus 51.9% subjects reported pain, 50.9% versus 39.4% subjects reported redness and 39.6% versus 36.5% reported swelling in Groups A and B, respectively.

Fever, drowsiness, irritability and loss of appetite were the most frequently reported solicited general symptoms per dose in the 7 days post vaccination period.

Following Dose 1, the reported frequency of fever (≥ 37.5°C) in 7 days period was 24.5% versus 20.2% in Groups A and B respectively. Following Dose 2, the reported frequencies were 71.2% and 67.3% respectively. The reporting frequency of fever/dose > 39°C was 1.9% versus 1.0% following Dose 1 in Groups A and B respectively and 17.3% versus 3.8% following Dose 2 in the 2 groups, respectively.

Overall, 58.5% versus 45.2% subjects reported drowsiness, 71.7% versus 57.7% subjects reported irritability, 66.0% versus 51.9% subjects reported loss of appetite and 77.4% versus 76.0% subjects reported fever (≥ 37.5°C) in Groups A and B respectively. A total of 18.9% versus 4.8% subjects in Group A and B respectively reported fever > 39°C.

The percentage of subjects reporting Grade 3 unsolicited AEs within the 42-day (Days 0–41) period was 3.8% versus 12.5% for Group A and Group B, respectively. A summary of solicited general symptoms is provided in Table 7, below:

Table 7. Summary of solicited general symptoms

Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose											
		3.75 µg/AS03A					1.9 µg/AS03B				
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Drowsiness	All	53	14	**26.4**	15.3	40.3	104	24	**23.1**	15.4	32.4
	Grade 3	53	2	**3.8**	0.5	13.0	104	0	**0.0**	0.0	3.5
Irritability	All	53	17	**32.1**	19.9	46.3	104	33	**31.7**	22.9	41.6
	Grade 3	53	5	**9.4**	3.1	20.7	104	2	**1.9**	0.2	6.8
Loss of appetite	All	53	17	**32.1**	19.9	46.3	104	25	**24.0**	16.2	33.4
	Grade 3	53	1	**1.9**	0.0	10.1	104	1	**1.0**	0.0	5.2
Temp (Axillary) (°C)	>= 37.5 °C	53	13	**24.5**	13.8	38.3	104	21	**20.2**	13.0	29.2
	> 38 °C	53	5	**9.4**	3.1	20.7	104	8	**7.7**	3.4	14.6
	> 38.5 °C	53	3	**5.7**	1.2	15.7	104	5	**4.8**	1.6	10.9
	> 39 °C	53	1	**1.9**	0.0	10.1	104	1	**1.0**	0.0	5.2
	> 39.5 °C	53	0	**0.0**	0.0	6.7	104	0	**0.0**	0.0	3.5
	> 40 °C	53	0	**0.0**	0.0	6.7	104	0	**0.0**	0.0	3.5
Dose 2											
Drowsiness	All	52	25	**48.1**	34.0	62.4	104	36	**34.6**	25.6	44.6
	Grade 3	52	2	**3.8**	0.5	13.2	104	0	**0.0**	0.0	3.5
Irritability	All	52	31	**59.6**	45.1	73.0	104	48	**46.2**	36.3	56.2
	Grade 3	52	4	**7.7**	2.1	18.5	104	3	**2.9**	0.6	8.2
Loss of appetite	All	52	30	**57.7**	43.2	71.3	104	44	**42.3**	32.7	52.4
	Grade 3	52	4	**7.7**	2.1	18.5	104	4	**3.8**	1.1	9.6
Temp (Axillary) (°C)	>= 37.5 °C	52	37	**71.2**	56.9	82.9	104	70	**67.3**	57.4	76.2
	> 38 °C	52	26	**50.0**	35.8	64.2	104	47	**45.2**	35.4	55.3
	> 38.5 °C	52	16	**30.8**	18.7	45.1	104	22	**21.2**	13.8	30.3
	> 39 °C	52	9	**17.3**	8.2	30.3	104	4	**3.8**	1.1	9.6
	> 39.5 °C	52	1	**1.9**	0.0	10.3	104	2	**1.9**	0.2	6.8
	> 40 °C	52	0	**0.0**	0.0	6.8	104	0	**0.0**	0.0	3.5
N= number of subjects with at least one administered dose; n/%= number/percentage of subjects reporting at least once the symptom when the intensity is maximum; 95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit											

One serious AE (SAE) was reported during the period covered by this report. Six days after the second dose of the vaccine, a 26 month old child suffered head trauma after a fall resulting in hospitalisation. The event was not considered related to the vaccine.

There were no withdrawals due to AEs in this study.

Evaluator's comment: The safety data suggest an increased reactogenicity after Dose 2 compared to Dose 1 of vaccine and with full dose compared to half dose vaccine.

Study 010

The safety analysis was performed on the TVC (N = 209).

During Days 0-7 post vaccination following any dose, the overall (all age groups) incidence of any solicited and unsolicited symptom (local and generalised) was 95.1%. This incidence was 72.3% and 91.6% for general and local solicited symptoms respectively.

During Days 0-7 post vaccination following any dose, a total of 97.1% subjects (all age groups) experienced any (at least one) solicited and solicited (local or general) symptom. This incidence was 98.1%, 100% and 95.0% in 3-5, 6-9 and 10-17 years age groups respectively. An overall total of 86.7 subjects experienced any (any least one) general solicited and unsolicited symptom in this period. This incidence was 84.9%, 87.7% and 87.0% in 3-5, 6-9 and 10-17 years age groups respectively. An overall total of 95.2% subjects experienced any (at least one) solicited and unsolicited local symptom in this period. This incidence was 92.5%, 98.2% and 95.0% in 3-5, 6-9 and 10-17 years age groups respectively.

The overall/dose incidence of any (local and generalised) Grade 3 symptoms (solicited and unsolicited) was 19.5%. The overall/subject incidence of any (local and generalised) Grade 3 symptoms (solicited and unsolicited) was 31.9%.

The incidence (%) of selected solicited symptoms (local and generalised) in Days 0-6 post vaccination by each dose and by subjects is provided in Table 8, below.

Table 8. Incidence (%) of selected solicited symptoms in Days 0-6 post vaccination, by dose and by subjects

(Study 010)	Dose 1			Dose 2			Subjects		
	3-5 y	6-9 y	10-17 y	3-5 y	6-9 y	10-17 y	3-5 y	6-9 y	10-17 y
Pain-local	75.5	94.7	92.9	84.6	96.5	96.8	88.7	98.2	96.9
Redness-local	28.3	24.6	21.4	34.6	33.3	28.0	41.5	38.6	33.7
Swelling-local	34.0	28.1	41.8	30.8	45.6	53.8	47.2	52.6	61.2
Fever ≥ 37.5°C	26.4	22.8	17.3	50.0	35.1	24.7	62.3	47.4	33.7
Drowsiness	20.8			32.7			41.5		
Irritability	26.4			28.8			39.6		
Arthralgia		15.8	26.5		22.8	36.6		35.1	44.9
Fatigue		36.8	44.9		50.9	53.8		7.0	64.3
Headache		43.9	49.0		45.6	54.8		59.6	71.4
Myalgia		26.3	35.7		28.1	50.5		40.4	57.1

Overall, 38.6% of the subjects reported at least one unsolicited AE (Days 0-20). The most frequently reported overall unsolicited AE was upper respiratory tract infection (11%). The Grade 3 unsolicited AE were reported in 7.5%, 3.5% and 1.0% subjects in 3-5 years, 6–9 years and 10-17 years age groups respectively.

AEs of specific interest, potential immune mediated diseases, and SAEs

None were reported up to Day 42 follow up.

> ***Evaluator's comment:*** The incidence of solicited AEs (local and general) was high across all age groups with a tendency towards higher occurrence after the second dose compared to the first dose. High rates to fever were experienced across all age groups indicating highly reactogenic vaccine. In the age group 3-5 years, the rates were 26.4% and 50% with Dose 1 and 2 respective with cumulative subject incidence of 62.3%. The report did not include any instance of febrile fits.

Study 023

The safety analysis was carried out on the TVC (N = 244) with 61, 65 and 118 subjects in the 3-5, 6-9 and 10-17 years age strata.

The overall/dose incidence of any (local and generalised) symptom (solicited and unsolicited) reported during Days 0-6 post vaccination was 76.7% (75.4%, 71.1% and 80.4% in the 3-5, 6-9 and 10-17 years age groups respectively).

The overall/subject incidence of any (local and generalised) symptom (solicited and unsolicited) reported during 0-6 days post vaccination was 84.4% (82.0%, 80.0% and 88.1% in 305, 6-9 and 10-17 years age groups respectively).

The incidence (%) of selected solicited symptoms (local and generalised) in Days 0-6 post vaccination by each dose and by subjects is provided in Table 9, below.

Table 9. Incidence (%) of selected solicited symptoms in days 0-6 post vaccination, by dose and by subjects

(Study 023)	Dose 1			Dose 2			Subjects		
	3-5 y	6-9 y	10-17 y	3-5 y	6-9 y	10-17 y	3-5 y	6-9 y	10-17 y
Pain-local	60.0	63.1	73.7	55.4	65.1	68.4	66.7	75.4	81.4
Redness-local	26.7	23.1	22.9	41.1	33.3	31.6	46.7	43.1	39.0
Swelling-local	21.7	23.1	30.5	28.6	25.4	25.6	36.7	33.8	39.0
Fever ≥ 37.5°C	31.7	15.4	10.2	35.7	12.7	18.8	45.0	20.0	25.4
Drowsiness	25.0			19.6			33.3		
Irritability	20.0			26.8			30.0		
Arthralgia		15.4	10.2		14.3	16.2		21.5	21.2
Fatigue		29.2	32.2		22.2	29.9		36.9	44.9
Headache		21.5	42.4		20.6	36.8		29.2	51.7
Myalgia		16.9	22.9		17.5	23.9		20.0	38.1

A total of 140 unsolicited AEs were reported during Days 0-42 (72, 26 and 42 in the 3-5, 6–9 and 41 10-17 years age strata respectively).

AEs of specific interest, potential immune mediated disease and SAEs

No AEs of specific interest or potential immune mediated disease was reported up to Day 42 follow up. Three SAEs reported in 3 subjects were not considered related to vaccination (urinary tract infection, facial bone fracture and fracture forearm).

Three adverse events leading to withdrawal were urticaria, pain and tonsillitis-pharyngitis.

> ***Evaluator's comment:*** The safety findings were consistent with those seen in the preceding Study 010. The dose effect with respect to reactogenicity is evident between the full dose (Study 010) and half dose (Study 023).

List of questions

The TGA provided the sponsor a copy of the clinical evaluation report, along with an invitation to provide a response to matters raised therein.

Initial clinical summary and conclusions

A single half dose (1.9 μg HA, ASO3 adjuvanted) led to an adequate homologous immune response in all age strata from 6 months of age to 17 years of age with respect to serological correlates of protection against influenza using HI assay, based on CHMP criteria for adults. Note that the immune correlates have not been validated for children.

This vaccine is available in a multidose vial presentation in two separate containers that require mixing before administration. The potential benefits of this vaccine include antigen sparing (requiring half the adult dose) and high immunogenicity (requiring single dose).

The Delegate's attention is drawn to the following two aspects in regard to the intended use of this vaccine in children and adolescents:

1. Pandemrix H1N1 vaccine was used during the 2009 H1N1 influenza pandemic in a number of countries. Over 30 million recipients are stated to have received this vaccine in Europe. The vaccine has not been used in Australia.

   The vaccine dosage in the currently approved Pandemrix H1N1 SmPC in Europe is a single 0.5 mL dose in persons 10 years old and above and a single 0.25 mL dose in the 6 months to 9 years old age group. This is consistent with the data.

   The proposed vaccine dosage in Australia is one or two doses of 0.5 mL in persons 10 years old and above and a single 0.25 mL dose in those 6 months to 9 years old. This is not consistent with the data.

   It is not clear what dosing guidelines were followed in children and adolescents during the 2009 pandemic use of this vaccine in Europe.

   Following this widespread use in Europe, a number of countries reported cases of narcolepsy, especially in children and adolescents, which led to a review of the association between Pandemrix and narcolepsy by the European Medicines Agency (EMA) at the request of European Commission.

   The EMA in its press release on 21 July 2011 concluded that in persons under 20 years of age, Pandemrix may only be used if the seasonal trivalent influenza vaccine is not available and if immunisation against H1N1 is still needed in a person at risk.

The EMA review considered studies carried out in Finland and Sweden, surveillance data from member states, and case reports from across the EU. The preliminary results of a collaborative study by the European Centre for Disease Prevention and Control (ECDC) and Vaccine Adverse Events Surveillance and Communication (VAESCO) were also considered.

The results indicate a 6 to 13 fold increased risk of narcolepsy with or without cataplexy in Pandemrix H1N1 vaccinated children and adolescents compared to unvaccinated children and adolescents. The risk was not found in individuals older than 20 years of age.

Genetic, environmental, and disease factors in association with Pandemrix H1N1 are thought to be involved. The investigations are ongoing and include a historical cohort study in Canada by the sponsor, where an equivalent vaccine, Arepanrix H1N1, was used.

In response to a request from the TGA for further information following the EMA announcement of restrictions on the use of Pandemrix H1N1 in children and adolescents in Europe, the sponsor stated it was not able to release the full EMA report to the TGA as it contained third party data.

The sponsor is proposing the following text to the Australian PI to account for the risk of narcolepsy:

Epidemiological studies relating to Pandemrix in two countries (Sweden and Finland) have indicated a six- to 13-fold increased risk of narcolepsy with or without cataplexy in vaccinated as compared with unvaccinated children/adolescents, corresponding to an absolute risk increase of about three to seven additional cases in 100,000 vaccinated subjects. This risk increase has not been found in adults (older than 20 years). A causal relationship between Pandemrix and narcolepsy has not been established.

Please also note that this application is accompanied by a Risk Management Plan (RMP) which is being reviewed by the Office of Product Review (OPR) within TGA. The OPR is also likely to provide further specific advice in relation to the narcolepsy issue.

2. As noted earlier, the validity and the relevance of immune correlates of influenza based on anti-HA response and the CHMP thresholds for use in children is unknown.

   This has been also a topic of recent deliberations among the European regulators[1]. A pre-publication copy of an article in this respect can be found at: <http://www.sciencedirect.com/science/article/pii/S0264410X11012266>

   Also, note that the studies included in the dossier were not final reports. In particular, assessment of neutralising antibodies data will be useful especially in view of uncertainty about the relevance and level of anti-HA response in children. In addition, full 3.75 μg adjuvanted dose recommended in the 10-17 years age group is not consistent with the data, which showed an adequate response with a 1.9 μg adjuvanted dose.

   In light of the above, the clinical evaluator is of the view that sufficient assurance of validity with respect to clinical efficacy and safety of this vaccine in children and adolescents cannot be reliably based on the data provided at this stage.

3. This monovalent ASO3 adjuvanted product was first registered in Australia in 2008 as a mock-up pandemic influenza vaccine Pandemrix H5N1 which was/is a non–circulating strain. Following the 2009 H1N1 influenza pandemic, the vaccine

[1] Granström M, Voordouw ACG. Registration of influenza vaccines for children in Europe. *Vaccine* 2011, 29(43): 7572-7575.

strain was updated to H1N1 in 2010. The WHO announced the end of the H1N1 pandemic on 10 August, 2010.

At present, A/H1N1 (2009) is the most prevalent circulating influenza strain the world over and the current status may be described as an inter-pandemic phase. The H1N1 (2009) strain is included in all seasonal trivalent influenza vaccines both in the southern and northern hemispheres. There is currently no official Australian recommendation to use any monovalent H1N1 pandemic vaccine for prevention of influenza.

The current regulatory status of Pandemrix H1N1 as a mock-up vaccine is also unclear as it now contains a specific circulating strain.

However, it is understood that in Australia, in the event of a future pandemic requiring an update of vaccine strain, immunogenicity and dose defining data will be required. Hence, the validity of the extension of usage for a mock up vaccine in the present phase is also in question.

Initial recommendation

The clinical evaluator does not support the requested extension of indication/dosing schedule to include use of Pandemrix in children and adolescents. Consequently all proposed changes to the PI are also not supported.

In addition, the following are recommended:

1. Based on the risk of narcolepsy in the identified population in Europe, the clinical evaluator recommends that the currently approved recommendation for use in *'Adults aged 18 years and older' should be modified to 'Individuals aged 20 years and older'*.
2. The currently recommended *'one or two doses of 0.5 mL' should be modified to 'single dose of 0.5 mL'*.

The Consumer Medicine Information (CMI) leaflet should be updated to reflect the intended changes in the PI.

Sponsor's response to the clinical evaluation report

In response to matters raised in the clinical evaluation report (see *List of Questions*, above), the sponsor commented that the original application contained interim study reports for the Studies 009, 010 and 023. Since that time, final study reports for these studies have become available, which provide data up to 12 months. This complete set of data is provided as supplementary data to further support the use of Pandemrix H1N1 in the paediatric population.

Supplementary clinical evaluation

A supplementary clinical evaluation report was prepared to take into account the sponsor's supplementary clinical data.

Overview of the supplementary data

Three clinical studies were included in the original submission (Studies 009, 010 and 023) with immunogenicity (HI) results at Day 42, that is, 21 days after Dose 2. The supplementary data provides Month 12 immunogenicity (HI) results for these 3 studies.

As described in the original submission (which contained interim clinical study reports), the Studies 010 and 023 in children aged 3-17 years were to be given a booster dose at

6 months using a 2+1 schedule. However, it appears now from the information provided in the supplementary data that a booster was not a part of the final design of Study 010 and it was not administered in Study 023.

Hence, the 12 months HI immunogenicity results now refer to persistence of antibodies at this timepoint following completion of 2 primary doses administered 3 weeks apart. In addition, results of viral (H1N1) micro neutralisation antibodies have also been provided for these studies. The results are described in brief as follows:

Efficacy

Study 009 (6-35 months old age group, 3 age strata; full dose versus half dose, 2+0 dosing schedule)

Group A (full (3.75 μg) dose group)

HI immune response

The overall (all age strata, that is, 6-11, 12-23, 24-35 months) SPR (with vaccine homologous HI antibody titre ≥ 1/40) was 100% at all timepoints; that is, on Day 21 (21 days after Dose 1), Day 42 (21 days after Dose 2) and Month 12 (indicating persistence of antibodies at 12 months).

Note all age strata had achieved 100% SPR at Day 21 as well as at Month 12.

The underlying GMTs peaked at Day 42. The values at this timepoint were 2068.2 (6-11 months age strata), 1909.3 (12-23 months age strata) and 1646.9 (24-35 months age strata). The GMTs declined significantly (by 6-9 times) at Month 12, ranging from 170.4 to 337.5 but were similar to values at Day 21 (ranging from 248.6 to 258.5).

H1N1 neutralising antibodies response

A total of 12.5% of children (all age strata) in this group were seropositive (≥ 1/8) for H1N1 neutralising antibodies at baseline, that is, pre-vaccination (8.3%, 0% and 40% in the 6-11, 12-23 and 24-35 months strata, respectively). The overall pre-vaccination mean neutralising antibodies titre was 5.7.

The Day 21 (that is, 21 days after Dose 1) neutralising antibodies titres were 44.4, 50.6, and 70.2 in the 3 age strata (6-11, 12-23 and 24-35 months), respectively.

The neutralising antibodies titres peaked at Day 42 (21 days after Dose 2) with values of 1950.4, 1575.2 and 2920.8 in the 3 age strata, respectively.

At Month 12, the neutralising antibodies titres declined to 674.1, 352.5 and 267.2 in the 3 age strata respectively, but were still many multiples of Day 21 values.

Group B (half (1.9 μg) dose group)

HI immune response

The overall (all age strata) SPR (as defined above) was 100% at all timepoints, that is, on Day 21 (21 days after Dose 1), Day 42 (21 days after Dose 2) and Month 12 (persistence of antibodies).

The underlying GMTs peaked at Day 42. The values at this timepoint were 1787.9 (6–11 months age strata), 1934.9 (12-23 months age strata) and 1587.2 (24-35 months age strata). The GMTs declined significantly (by 6-9 times) at Month 12, ranging from 163.9 to 226.2, but were similar to values at Day 21 (ranging from 223.5 to 249.8).

H1N1 neutralising antibodies response

A total of 7.0% of children (all age strata) in this group were H1N1 neutralising antibodies seropositive (≥ 1/8) at baseline (11.1%, 0% and 6.3% in 6-11, 12-23 and 24-35 months strata, respectively). The mean pre-vaccination neutralising antibodies titre was 5.6.

The Day 21 neutralising antibody titres were 53.4, 24.2 and 28.7 in the 3 age strata (6-11, 12-23 and 24-35 months), respectively.

The neutralising antibody titres peaked at Day 42 with values of 1554.6, 1345.8 and 1271.2 in the 3 age strata, respectively.

At Month 12, the neutralising antibody titres declined to 468.4, 150.4 and 327.4 in the 3 age strata, respectively, but were still many multiples of Day 21 values.

Vaccine response rate (neutralising antibodies)

Relatively lower neutralising antibodies titres were obtained at all timepoints in Group B (half dose) compared to Group A (full dose) across all age strata.

The vaccine response rates (VRR) with respect to H1N1 neutralising antibodies immune response (defined as the incidence rate of vaccines that have either a pre-vaccination titre < 1:8 and a post-vaccination titre ≥ 1:32 or a pre-vaccination titre < 1:8 and at least a 4 fold increase in post-vaccination titre) are shown in Table 10:

Table 10. H1N1 Neutralising antibody response – Vaccine Response Rate (ATP cohort for antibody kinetics, neutralising antibody subset)

009	Group A		Group B	
	VRR(%)	95%CI	VRR(%)	95%CI
Overall				
D21	65.2	42.7, 83.6	54.7	40.4, 68.4
D42	100	85.2, 100	98.1	90.1, 100
M12	100	84.6, 100	91.8	80.4, 97.7
6-11 months old				
D21	66.7	34.9, 90.1	56.0	34.9, 75.6
D42	100	73.5, 100	96.0	79.6, 99.9
M12	100	69.2, 100	86.4	65.1, 97.1
12-23 months old				
D21	66.7	22.3, 95.7	53.8	25.1, 80.8
D42	100	59.0, 100	100	76.8, 100
M12	100	59.0, 100	92.3	64.0, 99.8

009	Group A		Group B	
	VRR(%)	95%CI	VRR(%)	95%CI
24-35 months old				
D21	60.0	14.7, 94.7	53.3	26.6, 78.7
D42	100	39.8, 100	100	78.2, 100
M12	100	47.8, 100	100	76.8, 100

Study 010 (3-17 years old age group, 3 age strata, full dose only, 2+0 dosing schedule)

HI immune response

The SPR based on homologous HI antibody immune response was 100% at Days 21 and 42 in all age strata (3-5, 6-9 and 10-17 years) and persisted in the range 98-100% at Month 12.

The underlying titres peaked at Day 42 in all age strata. The GMT values at this timepoint were 1581.1 (3-5 years age strata), 964.6 (6-9 years age strata) and 1008.9 (10-17 years age strata). The GMTs declined significantly (by 4-12 times) at Month 12, ranging from 106.3 to 251.0 and were generally lower than Day 21 values (ranging from 168.3 to 547.9).

H1N1 neutralising antibodies response

Overall (all age strata), a total of 8.9% children were H1N1 neutralising antibodies seropositive (≥ 1/8) at baseline, that is, pre-vaccination (0%, 14.7% and 10.7% in the 3-5, 6-9 and 10-17 years strata, respectively). The overall mean pre-vaccination neutralising antibodies titre was 5.2.

The Day 21 neutralising antibodies titres were 64.3, 173.0 and 117.0 in the 3 age strata (3–5, 6-9 and 10-17 years), respectively.

The neutralising antibodies titres peaked at Day 42. The GMT values at this timepoint were 1345.7 (3-5 years age strata), 845.6 (6-9 years age strata) and 561.8 (10-17 years age strata).

The neutralising antibodies titres declined significantly (by 4-5 times) at Month 12 in all age strata. The Month 12 values were 168.4 and 118.1 in 6-9 and 10-17 years age strata respectively and were comparable to Day 21 values (173.0 & 117.0 in the 2 strata respectively). The Day 21, Day 42 and Month 12 values in 3-5 years age strata were 64.3, 1345.7 and 269.1, respectively.

The VRR (as defined previously: neutralising antibodies titres ≥ 1/32 or ≥ 4 fold rise) were as follows (Table 11):

Table 11. H1N1 Neutralising antibody response against A/Netherlands/602/9 up to Month 12 in Study 010 (ATP cohort for persistence, neutralising antibody subset)

	Overall		3-5 years		6-9 years		10-17 years	
	VRR (%)	95% CI	VRR (%)	95% CI	VRR (%)	95% CI	VRR (%)	95% CI
D21	86.4	77.4, 92.8	81.5	61.9, 93.7	90.9	75.7, 98.1	85.7	67.3, 96.0
D42	100	95.8, 100	100	85.8, 100	100	89.4, 100	100	87.7, 100
M12	95.2	88.1, 98.7	100	85.8, 100	96.8	83.3, 99.9	89.3	71.8, 97.7

Study 023 (3-17 years old age group, 3 age strata; half dose only; 2+0 dosing schedule)

In this study the participants were divided into two blood sampling schedules (BS1 and BS2). The HI immune response at Days 21 and 42 in BS1 Group were reported earlier and included in the original clinical evaluation report. The earlier report also included Day 42 response in BS2 group.

The supplementary data include Month 12 results in BS2 group for HI immune response. The H1N1 neutralising antibodies results for BS1 at pre-vaccination, Day 21, Day 42 and Month 12 have also been provided. The H1N1 neutralising antibodies results for BS2 are at Months 6 and 12.

HI immune response - BS2 Group

At Month 12 in the BS2 Group, the overall (all age strata) SPR based on homologous HI antibody immune response at Month 12 was 87.4%. The age strata specific SPRs were 85.0%, 84.6% and 90.2% in 3-5, 6-9 and 10-17 years groups respectively. The reported rates at this timepoint were thus lower than those in the preceding full dose study (Study 010; 98-100%).

Note the reported SPR at Day 42 (21 days after Dose 2) in both BS1 and BS2 groups were 100% across all strata. The Day 21 (21 days after Dose 1) reported in BS1 ranged from 98–100% (from original clinical study report).

At Month 12, the underlying HI antibody titres (GMTs) showed a significant drop from Day 42 levels as follows (Table 12):

Table 12. HI antibody response (GMT) against vaccine-homologous A/California/7/2009 (H1N1)v-like in Study 023 (BS2 group; ATP cohort for antibody persistence at Month 12)

	Overall	3-5 years	6-9 years	10-17 years
D42	1108.8	1490.9	1104.6	1135.2
M12	83.3	48.5	60.5	132.8

The Day 42 titres in BS1 and BS2 groups were comparable (from original study report).

H1N1 neutralising antibodies response - BS1 Group

Overall (all age strata), a total of 26.6% children were H1N1 neutralising antibodies seropositive (≥ 1/8) at baseline (18.8%, 31.3% and 28.1% in the 3-5, 6-9 and 10-17 years strata respectively). The overall mean pre-vaccination neutralising antibodies titre was 6.3.

The Day 21 neutralising antibodies titres were 27.7, 65.9 and 72.4 in the 3 age strata (3-5, 6-9 and 10-17 years) respectively.

The neutralising antibodies titres peaked at Day 42. At this timepoint (21 days after Dose 2) the reported values were 433.2 (3-5 years age strata), 473.7 (6-9 years age strata) and 344.1 (10-17 years age strata). The titres declined significantly at Month 6 in all age strata. The Month 6 values were 158.9, 203.7 and 141.3 in 3-5, 6-9 and 10-17 years age strata respectively but remained higher than Day 21 levels.

The VRR (as defined previously, neutralising antibodies titres ≥ 1/32 or ≥ 4 fold rise) were as follows (Table 13):

Table 13. H1N1 Neutralising antibody response against A/Netherlands/602/9 up to Month 6 (ATP cohort for antibody persistence at Month 12, BS1)

	Overall		3-5 years		6-9 years		10-17 years	
	VRR (%)	95%CI	VRR (%)	95%CI	VRR (%)	95%CI	VRR (%)	95%CI
D21	61.7	48.2, 73.9	50.0	24.7, 75.3	71.4	41.9, 91.6	63.3	43.9, 80.1
D42	100	94.1, 100	100	78.2, 100	100	78.2, 100	100	88.8, 100
M6	91.9	82.2, 97.3	100	79.4, 100	93.3	68.1, 99.8	87.1	70.2, 96.4

H1N1 neutralising antibodies response - BS2 Group

The reported neutralising antibodies levels (GMTs) at Day 42 and Months 6 and 12 were as follows (Table 14):

Table 14. H1N1 Neutralising antibody response (GMT) against A/Netherlands/602/9 up to Month 12 (ATP cohort for antibody persistence at Month 12, BS2)

	Overall	3-5 years	6-9 years	10-17 years
D42	289.1	470.0	310.2	173.5
M6	155.7	142.9	164.7	159.9
M12	139.5	152.3	129.9	138.3

The vaccine response rates were not calculated as blood sampling in this group was done from Day 42.

Safety

No new safety findings, including onset of chronic or immune disorder, in relation to vaccination were reported up to follow up at Month 12. A list of SAEs reported up until Month 12 in the 3 Studies is provided in Table 15, below:

Table 15. Listing of SAEs reported up to Month 12 in Studies 009, 010 and 023 (TVC)

Study	Study vaccine	Age at onset	Gender	Preferred term	Day of onset relative to previous dose	Causality	Outcome
D-Pan-H1N1-009	3.75 µg HA/AS03A	10 months	Male	Asthma	55 days post dose 2	Not related	Recovered/resolved
		11 months	Male	Bronchopneumonia	84 days post dose 2	Not related	Recovered/resolved
		18 months	Female	Viral rash	60 days post dose 2	Not related	Recovered/resolved
		26 months	Female	Traumatic brain injury	6 days post dose 2	Not related	Recovered/resolved
		16 months	Male	Lymphadenitis	226 days post dose 2	Not related	Recovered/resolved
		15 months	Male	Bronchitis	107 days post dose 2	Not related	Recovered/resolved
		18 months	Male	Bronchospasm	213 days post dose 2	Not related	Recovered/resolved
	1.9 µg HA/AS03B	14 months	Male	Bronchitis	64 days post dose 2	Not related	Recovered/resolved
		11 months	Male	Bronchiolitis	108 days post dose 2	Not related	Recovered/resolved
				Conjunctivitis	108 days post dose 2	Not related	Recovered/resolved
				Otitis media	108 days post dose 2	Not related	Recovered/resolved
D-Pan-H1N1-010	3.75 µg HA/AS03A	11 years	Male	Bone marrow failure	120 days post dose 2	Not related	Not recovered/not resolved
D-Pan-H1N1-023	1.9 µg HA/AS03B	4 years	Female	Urinary tract infection	11 days post dose 1	Not related	Recovered/resolved
		16 years	Female	Ectopic pregnancy	52 days post dose 2	Not related	Recovered/resolved
		15 years	Male	Facial bones fracture	4 days post dose 1	Not related	Recovered/resolved
		12 years	Male	Asthma	37 days post dose 2	Not related	Recovered/resolved
		11 years	Female	Ranula	194 days post dose 2	Not related	Not recovered/not resolved
		4 years	Female	Febrile infection	46 days post dose 2	Not related	Recovered/resolved
				Haematoma	46 days post dose 2	Not related	Recovered/resolved
		8 years	Female	Forearm fracture	11 days post dose 2	Not related	Recovered/resolved

Final clinical summary and conclusions

The supplementary data consisted of HI immune response results at Month 12 and neutralising antibodies results at all timepoints for all 3 studies. The planned administration of booster dose at 6 months in Studies 010 and 023 was not carried out.

The supplementary data support the findings and conclusions in the original clinical evaluation report (see above under *Supplementary Clinical Evaluation*). As noted previously, the results obtained in the 3 clinical trials indicate that a single 1.9 µg dose may provide adequate (HI) immune response in all age groups from 6 months to 17 years. However, use of full (3.75 µg) dose in 10-17 years age group, as proposed by the sponsor, is also supported by the data.

The protective thresholds for HI immune response have not been validated in children. However, the results for functional antibodies, that is, H1N1 neutralising antibodies provide useful reassurance and were consistent with the HI immune response. The protective levels of neutralising antibodies are also not known and may vary from 1/20 to as much as 1/80 dilution (convalescent serum levels). There is also the issue of lack of standardisation of assay methodology.

In view of relatively lower vaccine response rates with respect to neutralising antibodies at Day 21 (that is, after single dose), especially in infants and young children ages 6-35 months, a recommendation to complete 2-dose course is also supported. The actual use will be dependent on the dynamics of a pandemic and actual instructions issued by the authorities at such time.

The use of this vaccine in Europe during the H1N1 2009 influenza pandemic has been shown to be associated with 6-13 fold higher risk of narcolepsy in recipients under the age of 20 years. Consequently, in Europe the use of this vaccine has now been restricted to adults above 20 years of age. Note that current approval in Australia is for adults above 18 years of age.

It may also be noted that at present only unadjuvanted influenza vaccines are being used in children for protection against seasonal influenza. Although, Pandemrix H1N1 is intended for use in officially declared pandemic situations only and is not expected to involve more than 1 to 2 administrations, the consequences of any subsequent and repeated use are also unknown.

Although, the vaccine has desirable utility features in a pandemic situation such as dose sparing and has also shown adequate, *albeit* clinically unvalidated immunogenicity in

children, given the risk of narcolepsy and availability of other vaccines, the evaluator was of the view that there is no compelling case to recommend use in children at present.

It may be appropriate, however, to update the clinical trials section of the Australian PI to include results of Studies 009, 010 and 023.

Final recommendation

The sponsor's application to include dosing recommendations for use in children 6 months to 17 years of age is not recommended. All conclusions and recommendations in the original clinical evaluation report remain valid (see above under *Initial clinical summary and conclusions*).

The following text is recommended for inclusion in the Pandemrix H1N1 Australian PI with respect to the risk of narcolepsy:

> *Epidemiological studies relating to Pandemrix in two countries (Sweden and Finland) have indicated a 6 to 13-fold increased risk of narcolepsy with or without cataplexy in vaccinated as compared with unvaccinated children/adolescents. This risk increase has not been found in adults older than 20 years.*

This statement should also be included in the Pandemrix CMI.

Details of other recommendations regarding revisions to the PI are beyond the scope of this AusPAR.

V. Pharmacovigilance findings

Risk management plan

The sponsor has provided a RMP (Table 16) which is in accordance with the *CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine* (EMEA/359381/2009; revision 1.1 adopted by CHMP on 24 September 2009).

Table 16. Summary of RMP. Table continued across three pages.

Potential theoretical safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Anaphylaxis	• Enhanced pharmacovigilance o Weekly signal detection o Use of targeted follow-up questionnaires o Individual reports expedited to regulators o Included in Table 3 of simplified PSURs† o Cumulative analysis included in full PSUR following end of pandemic period o Ad hoc analyses if reporting rate exceeds 1/100,000 doses distributed • Incidence will be estimated in participants of the post-authorisation safety study	• Contraindication in the proposed labelling • Precaution in the proposed labelling regarding use in persons with known hypersensitivity, other than anaphylaxis, to vaccine components
Autoimmune hepatitis	• Enhanced pharmacovigilance o Weekly signal detection o Use of targeted follow-up questionnaires o Individual reports expedited to regulators o Cumulative analysis included in full PSUR following end of pandemic period o Ad hoc analyses if reporting rate exceeds 20/100,000 doses distributed	NA*
Bell's palsy	• Enhanced pharmacovigilance o Weekly signal detection o Use of targeted follow-up questionnaires o Individual reports expedited to regulators o Included in Table 3 of simplified PSURs o Cumulative analysis included in full PSUR following end of pandemic period o Ad hoc analyses if reporting rate exceeds 24/100,000 doses distributed • Incidence will be estimated in participants of the post-authorisation safety study	NA

Potential theoretical safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Convulsion	• Enhanced pharmacovigilance o Weekly signal detection o Use of targeted follow-up questionnaires o Individual reports expedited to regulators o Included in Table 3 of simplified PSURs o Cumulative analysis included in full PSUR following end of pandemic period o Ad hoc analyses if reporting rate exceeds 3,000/100,000 doses distributed • Incidence will be estimated in participants of the post-authorisation safety study	NA
Demyelinating disorders	• Enhanced pharmacovigilance o Weekly signal detection o Use of targeted follow-up questionnaires o Individual reports expedited to regulators o Included in Table 3 of simplified PSURs o Cumulative analysis included in full PSUR following end of pandemic period o Ad hoc analyses if reporting rate exceeds published incidence rate • Incidence will be estimated in participants of the post-authorisation safety study	NA
Encephalitis	• Enhanced pharmacovigilance o Weekly signal detection o Use of targeted follow-up questionnaires o Individual reports expedited to regulators o Included in Table 3 of simplified PSURs o Cumulative analysis included in full PSUR following end of pandemic period o Ad hoc analyses if reporting rate exceeds 7/100,000 doses distributed • Incidence will be estimated in participants of the post-authorisation safety study	NA

Potential theoretical safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Guillain-Barré syndrome	• Enhanced pharmacovigilance o Weekly signal detection o Use of targeted follow-up questionnaires o Individual reports expedited to regulators o Included in Table 3 of simplified PSURs o Cumulative analysis included in full PSUR following end of pandemic period o Ad hoc analyses if reporting rate exceeds 2/100,000 doses distributed o Active monitoring in collaboration with national groups/agencies • Incidence will be estimated in participants of the post-authorisation safety study • Study to establish a case-series in France, with possibility for case-control analysis, if needed	NA
Increased concentrations of hepatic enzymes	• Enhanced pharmacovigilance o Weekly signal detection o Use of targeted follow-up questionnaires o Individual reports expedited to regulators o Cumulative analysis included in full PSUR following end of pandemic period o Ad hoc analyses if signal detected	NA
Neuritis	• Enhanced pharmacovigilance o Weekly signal detection o Use of targeted follow-up questionnaires o Individual reports expedited to regulators o Included in Table 3 of simplified PSURs o Cumulative analysis included in full PSUR following end of pandemic period o Ad hoc analyses if reporting rate exceeds published incidence rate • Incidence will be estimated in participants of the post-authorisation safety study	NA

Potential theoretical safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Vasculitis	• Enhanced pharmacovigilance o Weekly signal detection o Use of targeted follow-up questionnaires o Individual reports expedited to regulators o Included in Table 3 of simplified PSURs o Cumulative analysis included in full PSUR following end of pandemic period o Ad hoc analyses if reporting rate exceeds 2/100,000 doses distributed • Incidence will be estimated in participants of the post-authorisation safety study	NA
Vaccination failure	• Enhanced pharmacovigilance o Weekly signal detection o Use of targeted follow-up questionnaires o Individual reports expedited to regulators o Included in Table 3 of simplified PSURs o Cumulative analysis included in full PSUR following end of pandemic period • Incidence will be estimated in participants of the post-authorisation safety study	NA
Vaccine effectiveness	• GSK Biologicals will support ECDC vaccine effectiveness project • GSK Biologicals will obtain results from the UK HPA project	
Fever in children	• Additional clinical trials (H1N1-009, H1N1-010, H1N1-012, H1N1-023, H1N1-025) • Routine pharmacovigilance • Cumulative analysis in full PSUR prepared after the pandemic period	• No inclusion of children in the indication section of the proposed labelling • Statement in proposed labelling that there is no experience in children
Missing data in pregnant women	Routine pharmacovigilance, including follow-up of cases of pregnancy: • spontaneously reported by patients and HCPs • enrolled/observed during post-authorisation safety study • observed during clinical trials • reported via Pregnancy Registry	NA

Potential theoretical safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Missing data in children	Conduct additional clinical trials • H1N1-009 (6 to 35 months) • H1N1-010 (3 to 17 years) • H1N1-012 (2 to 5 months) • H1N1-023 (3 to 17 years) • Post-authorisation safety study (depending on UK vaccination policy)	• No inclusion of children in the indication section of the proposed labelling • Statement in proposed labelling that there is no experience in children
Limited data in subjects with compensated underlying conditions; No data in subjects with severe underlying medical conditions and immunocompromise	• Routine pharmacovigilance • Post-authorisation cohort study: individuals will be included based on national recommendations, underlying medical conditions will be documented for *post hoc* analyses	NA

* NA = not applicable; † PSUR = periodic safety update report

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Safety specification

A summary of the Ongoing Safety Concerns as discussed by the sponsor is as follows:

Important identified risks:

- Fever in children

Important potential risks:

- Adverse events of special interest
  - anaphylaxis
  - Bell's palsy
  - convulsion
  - demyelinating disorders
  - encephalitis
  - Guillain-Barre syndrome (GBS)
  - neuritis
  - vasculitis
  - vaccination failure
- Autoimmune hepatitis and increased concentrations of hepatic enzymes

Important missing information:

- Safety data in pregnant women, individuals with clinically severe underlying medical conditions, and immunocompromised individuals
- Limited safety data in children
- Efficacy or effectiveness, which is not possible to evaluate prior to use

Pharmacovigilance plan

The sponsor has provided the details of their standard pharmacovigilance activities which they undertake outside of an officially-declared H1N1 influenza pandemic. The routine activities form the foundation for the modified activities that the sponsor will undertake during an H1N1 influenza pandemic.

In addition to the proposed routine activities, the sponsor has provided details of the activities they will undertake in an H1N1 influenza pandemic. The details of the additional pharmacovigilance activities proposed by the sponsor comply with the *CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine.* However, as the RMP is a global document it is not clear if the sponsor intends to implement any of the additional pharmacovigilance activities in Australia.

Risk minimisation activities

The sponsor has provided the following evaluation of the need for risk minimisation activities: *"Product labelling is an important tool for risk communication and risk minimisation. The proposed labelling clearly outlines contraindications and precautions for use of the candidate vaccine. In addition to labelling, risk minimisation activities are proposed for two potential risks: medical errors and contamination of the multipledose vials."* This is acceptable.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; it is recommended that the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration. In addition, it is recommended that:

- the sponsor be required to comment of the association between Pandemrix and injection site discolouration reported in the Netherlands Pharmacovigilance Centre newsletter *Lareb*[2],and provide evidence to support why this should not be included as a potential risk in the summary of Ongoing Safety Concerns.
- the sponsor update the RMP to include narcolepsy in children and adolescents below the age of 20 years as an important potential risk. This request is based on results from a Swedish registry based cohort study which indicated a 4 fold increased risk of narcolepsy in vaccinated children and adolescents below the age of 20 years vaccinated with Pandemrix, compared to children of the same age that were not vaccinated. Supported by findings from epidemiological studies in Sweden and France which indicated a 4-9 fold increased risk of narcolepsy in vaccinated as compared to unvaccinated children/adolescents. The sponsor should also propose pharmacovigilance and risk minimisation activities and update the relevant sections of the RMP.
- the sponsor be required to provide details of the additional pharmacovigilance activities that will be implemented in Australia in the event of an officially-declared H1N1 pandemic. In order to retain the global RMP, it would be strongly recommended that these details be provided in an Australian-specific annex to the RMP. Specifically it is recommended that:

[2] The Netherlands Pharmacovigilance Centre, Lareb Newsletter number 5, May 2011

  - the sponsor confirm that simplified PSURs will be submitted to the TGA and that these simplified PSURs will contain a summary of AEs and vaccine distribution in Australia.
  - as the number of reports of GBS is anticipated to be very small, rather than undertake an Australian specific activity such as a case series or registry for GBS (as outlined in the CHMP guidelines), the sponsor commit to informing the TGA within 72 h of any reported cases of GBS.
  - the sponsor provide a protocol for a Post Authorisation Safety Study (PASS) in Australian subjects that could be implemented, if required, in Australia in the event of a pandemic. Such circumstances where the sponsor may be required to undertake an Australia specific PASS could be if the pandemic spread rapidly through the southern hemisphere before spreading to the northern hemisphere and subsequently the vaccine is rolled out in the southern hemisphere earlier than the northern hemisphere. It is acknowledged that it would be difficult to develop a protocol for a PASS in the RMP response time period and therefore, it is recommended that such a protocol be developed in consultation with the OPR and submitted to the TGA within 12 months of registration.

- the sponsor provide information on whether there are plans to use the proposed instructional materials to reduce the potential for medication errors in Australia in the event that an H1N1 pandemic is officially declared. Furthermore, the sponsor should provide comments of how they will ensure that the instructional materials will be received and understood by the end users of the vaccine.
- the sponsor be required to confirm that the risk minimisation activities proposed in the RMP will be undertaken in Australia, and if so, the sponsor should provide copies of the instructional materials that will be used in Australia. If the sponsor is not proposing to undertake these risk minimisation activities in Australia, it is recommended that they be required to provide a justification for this decision.
- in regard to the proposed routine risk minimisation activities, the evaluator recommended revisions to the PI and CMI (details of these are beyond the scope of this AusPAR).

Issues raised by the RMP evaluator were addressed in the *Response from Sponsor,* below.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Data from the initial submission

Clinical data only were submitted. The originally submitted data comprises of immunogenicity data (HI immune responses) from three clinical studies (Studies 009, 010 and 023). Study 009 was carried out in children 6-35 months, whereas Studies 010 and 023 were carried out in children 3-17 years of age.

Study 009 was a randomised, multicentre, open label immunogenicity study of Pandemrix H1N1 pandemic influenza vaccine in healthy children aged 6 months to 35 months. This study was conducted in Spain in 2009-10. A total of 157 subjects were included in the TVC and were allocated in 2:1 ratio to Group A (full adult dose of 3.75 μg HA/AS03$_A$, n = 53) and Group B (half adult dose with 1.9 μg HA/AS03$_B$, n = 104). The study subjects received primary vaccination which consisted of two IM injections 3 weeks apart, on Day 0 and Day 21. The primary objective was to evaluate homologous HI immune response with respect to the CHMP criteria, using adult correlates, at Day 42 after Dose 1 (that is, 21 days after Dose 2).

The results showed that following the first dose of the half-dose vaccine (1.9 μg HA/AS03$_B$), the homologous HI immune response in these children exceeded the CHMP criteria for adult thresholds. Dose 2 further augmented the immune response. The evaluator pointed out that the significance of the Dose 2 response is not clear, as is the relevance of adult immune criteria for use in children. The results for neutralising antibodies were not submitted in the initial dossier but were later provided in the supplementary data.

The safety data suggest an increased reactogenicity after Dose 2 compared to Dose 1 of vaccine and with full dose compared to half dose vaccine.

Study 010 was an open label, multicentre, non-randomised immunogenicity study conducted in healthy children 3-17 years of age. This study was conducted in Spain in 2009. The initial abridged study report comprises immunogenicity results following the primary vaccination which includes the first full dose (3.75 μg HA/AS03$_A$ at Day 0) and the second full dose (at Day 21) of Pandemrix H1N1 pandemic vaccine. The study also planned to have a booster dose at Month 6 but was not later carried out. A total of 210 healthy children, stratified to 3 age strata (3-5, 6-9 and 10-17 years), were enrolled in the study. A total of 198 subjects were included in the ATP cohort for immunogenicity with 51, 55 and 92 in the 3-5, 6-9 and 10-17 age group, respectively.

Adequate homologous HI immune response in all age strata was achieved following single full dose of vaccine (3.75 μg HA/AS03$_A$) with respect to the CHMP criteria using adult thresholds. The Day 42 results (21 days following Dose 2) showed further accentuation of the immune response. The evaluator commented that the clinical need for the second dose is uncertain in view of the satisfactory immune response to Dose 1.

The incidence of solicited AEs (local and general) was high across all age groups with tendency towards higher occurrence after second dose compared to first dose. High rates of fever were experienced across all age groups, indicating highly reactogenic vaccine.

Study 023 was an open-label, multicentre, non-randomised immunogenicity study conducted in healthy children 3-17 years of age. This study was conducted in Germany in 2009. The abridged report comprises the immunogenicity results following completion of primary vaccination (first and second dose) with the half dose of the Pandemrix H1N1 vaccine (1.9 μg HA/AS03$_B$) on Day 1 and Day 21, respectively. The booster dose at Month 6 was planned but was not carried out. A total of 245 healthy children were allocated in a 1:1:2 ratio to three age strata (3-5, 6-9 and 10-17 years). The primary objective was to evaluate homologous antibody immune response after two half doses of Pandemrix H1N1

vaccine (1.9 μg HA/AS03$_B$). The age groups in this study are the same as those in Study 010. A total of 225/245 (92%) subjects were included in the ATP cohort for immunogenicity, with 54, 60 and 111 in the 3 age strata, respectively.

The subjects were also randomised (1:1) to one of the two blood sampling schedules (BS1 and BS2). The blood samples were collected on Days 0, 21, 42 and Month 6 in BS1, and on Day 42, Month 6, Month 6/7 and Month 12 in BS2. At the time of reporting, the results are available for all time-points in BS1 group (Days 0, 21 and 42) and for Day 42 in BS2 group.

For BS1, the overall SPR was 6.3% pre-vaccination, 99.1% at Day 21 after Dose 1, and 100% overall and in each age stratum at Day 42 (21 days after second dose). For BS2, the SPR at Day 42 was 100% overall and in each age stratum.

For BS1, the overall SCR at Day 21 and Day 42 was 98.2% and 99.1% respectively (100% at Day 21 and Day 42 for the 3-5 and the 6-9 years age group, and 96.3% at Day 21 and 98.1% at Day 42 for the 10-17 years age group).

The overall GMFR in BS1 group was 40.87 at Day 21 and 151.82 at Day 42 (33.62 at Day 21 and 237.68 at Day 42 for the 3-5 years age group; 36.33 at Day 21 and 185.25 at Day 42 for the 6-9 years age group; and 48.29 at Day 21 and 107.74 at Day 42 for the 10-17 years age group).

The results showed that following the first dose of the vaccine at half adult dose (1.9 μg HA/AS03$_B$) in these children (3-17 years), all CHMP criteria were satisfactorily achieved using adult thresholds. This study demonstrated that a single half dose (1.9 μg HA/AS03$_B$) was able to elicit adequate immune response in the 10-17 years age group.

The safety findings in this study were consistent with those seen in Study 010. The dose effect with respect to reactogenicity is evident between the full dose (Study 010) and half dose (Study 023).

Supplementary data

In response to the clinical evaluation report, the sponsor provided supplementary data which consisted of HI response results at Month 12 and neutralising antibodies results at Day 21, Day 42 and Month 12 for the three studies.

As described in the original submission, the children (3-17 years old) in Studies 010 and 023 were to be given a booster dose at 6 months, however, the supplementary data indicate that the booster dose was not considered necessary and was therefore not carried out. The immunogenicity results at Month 12 are therefore referring to the persistence of antibodies at this timepoint following completion of 2 primary doses at Day 0 and Day 21.

The HI and neutralising antibodies results for the 3 studies were discussed in detail in the clinical evaluation of the supplementary data. Overall, both the HI and neutralising antibodies responses peaked at Day 42 and declined significantly at Month 12. The HI responses showed that the CHMP criteria were still all met at Month 12. No new safety signals were detected.

Vaccine response rate is defined as the incidence rate of vaccines that have either a pre–vaccination neutralising antibodies titre <1:8 and a post-vaccination neutralising antibodies titer ≥ 1:32 or a pre-vaccination titre ≥ 1:8 and at least a 4 fold increase in post–vaccination titre. The results showed that VRR is relatively lower after the first dose (at Day 21) than after the second dose (at Day 42) for both the full dose and the half dose groups.

As noted in the evaluation of the original submission, the results obtained from 3 clinical trials indicate that a single half dose (1.9 μg HA/AS03$_B$) may provide adequate HI response

in all age groups from 6 months to 17 years. However, use of full dose (3.75 μg) in the 10–17 years age group, as proposed by the sponsor, is also supported by the data.

In view of the relatively lower VRR with respect to the neutralising antibodies after the first dose, especially in infants and young children ages 6-35 months, a recommendation to complete a 2-dose course is also supported. The actual use will be dependent on the dynamics of a pandemic and actual instructions issued by the authorities at such time.

The evaluator has pointed out that the protective thresholds for HI response have not been validated in children and that the protective levels of neutralising antibodies are also not known and may vary from 1/20 to as much as 1/80 dilution (convalescent serum levels). There is also the issue of a lack of standardisation of assay methodology with neutralising antibodies.

Clinical evaluator's recommendation

The clinical evaluator raised the issue of narcolepsy cases reported in children and adolescents following the widespread use of Pandemrix H1N1 vaccine in Europe and the results of the CHMP review in relation to the narcolepsy case reports. In view of the increase risk of narcolepsy associated with the use of Pandemrix H1N1 vaccine and the available seasonal influenza vaccines containing the A/California/7/2009(H1N1)v-like strain, the clinical evaluator does not support the requested inclusion of children and adolescents in the dosing schedule and the usage population in the PI of Pandemrix H1N1 vaccine.

Risk management plan

RMP version 5.0, dated February 2010 was submitted as part of this submission and was evaluated by the OPR. The sponsor was requested to update the RMP to include narcolepsy in children and adolescents below the age of 20 years as an important potential risk. The sponsor responded that RMP version 10 has been updated to include narcolepsy. However, this updated RMP has not been provided to TGA for evaluation. Instead, the sponsor stated that the RMP version 10 will be submitted before distribution of the first doses in Australia. This response was considered as unacceptable by the OPR. The sponsor was also requested to provide details of the additional pharmacovigilance activities that they would undertake in Australia in the event of a pandemic. A very limited justification for the sponsor's decision not to undertake Australian specific pharmacovigilance activities for the Pandemrix H1N1 vaccine was provided to the TGA. This response was considered to be unacceptable by the OPR.

In the light of the sponsor's response and the lack of Australian specific pharmacovigilance activities, the OPR evaluator was concerned that there are not sufficient activities to monitor the use of this vaccine and to ensure its safety in an Australian population, specifically in paediatric populations. This is particularly pertinent given the recent Northern hemisphere experience where Pandemrix has been shown to be associated with narcolepsy in paediatric populations aged to 20 years.

It was further noted by the evaluator that the currently approved indication for Pandemrix includes adults aged 18-20 years. The evaluator requested the sponsor should be required to implement a RMP with pharmacovigilance and risk minimization activities to mitigate against the potential risk of narcolepsy in 18-20 year olds.

As discussed above, the sponsor's response to the recommendations in the RMP evaluation report was not considered acceptable by the OPR.

The sponsor addressed the RMP issues highlighted in this section in their Pre Advisory Committee on Prescription Medicines (ACPM) response (see *Response from sponsor*).

Risk-benefit analysis

Delegate considerations

The reported risk of narcolepsy associated with Pandemrix H1N1 vaccine

Pandemrix H1N1 vaccine has been registered in Australia since 2010 but has not been used following registration. The vaccine was used extensively in Europe during H1N1 pandemic in late 2009 and early 2010. Following the widespread use in Europe during that period, cases of narcolepsy were reported, which led to a review of the association between Pandemrix and narcolepsy by the EMA. The reported cases of narcolepsy occurred during a pandemic period, while the EMA review has been conducted in the context of seasonal use.

The EMA review considered epidemiological studies carried out in Finland and Sweden, surveillance data from member states, and case reports from across the EU. The preliminary results of a collaborative study by the ECDC and VAESCO were also considered. The EMA's CHMP considered that the epidemiological studies in Finland and Sweden were well designed. The study results indicate a 6 to 13 fold increased risk of narcolepsy with or without cataplexy in vaccinated as compared with unvaccinated children/adolescents, corresponding to about an additional 3 to 7 cases in every 100,000 vaccinated subjects. This risk increase has not been found in adults (older than 20 years). The committee noted that the vaccine is likely to have interacted with genetic or environmental factors which might raise the risk of narcolepsy and that other factors may have contributed to the results. The investigations are still ongoing. The following restrictions were included in the EU SmPC for Pandemrix H1N1 vaccine: *"In persons under 20 years of age, Pandemrix should only be used if the recommended annual seasonal trivalent influenza vaccine is not available and if immunisation against (H1N1)v is considered necessary."*

The sponsor is proposing the following text to the Australian PI in relation to the risk of narcolepsy: *"Epidemiological studies relating to Pandemrix in two countries (Sweden and Finland) have indicated a six- to 13-fold increased risk of narcolepsy with or without cataplexy in vaccinated as compared with unvaccinated children/adolescents, corresponding to an absolute risk increase of about three to seven additional cases in 100,000 vaccinated subjects. This risk increase has not been found in adults (older than 20 years). A causal relationship between Pandemrix and narcolepsy has not been established."*

The questionable current need for Pandemrix H1N1 vaccine

The WHO announced the end of the H1N1 pandemic in August 10, 2010. Although the A/California/7/2009(H1N1)v-like strain is still currently the most prevalent circulating influenza stain, all seasonal trivalent influenza vaccines in southern and northern hemispheres have included the A/California/7/2009(H1N1)v-like strain. There is currently no official Australian recommendation to use any monovalent H1N1 pandemic vaccine for prevention of influenza. It may also be noted that at present only unadjuvanted influenza vaccines are being used in children for protection against seasonal influenza.

Based on the above facts, the current need for the Pandemrix H1N1 vaccine is questionable.

Delegate's proposed action

The Delegate proposes the following actions in relation to this application:

In view of the increased risk of narcolepsy associated with the use of Pandemrix H1N1 vaccine in people under the age of 20 and the availability of other influenza vaccine against the 2009 H1N1 viral strain, the benefits and risks balance is not considered

favorable for the use of Pandemrix H1N1 vaccine in children and adolescents. The sponsor's request to include a dosing schedule for children and adolescent (6 months to 17 years) is therefore not recommended.

In addition, it is proposed to modify the currently approved recommendation for use in *'adults aged 18 years and older'* to *'individuals aged 20 years and older'*. Alternatively, the PI should include the following statement: *"In persons under 20 years of age, Pandemrix should only be used if the recommended annual seasonal trivalent influenza vaccine is not available and if immunisation against (H1N1)v is considered necessary."*

To address the increased risk of narcolepsy, the following text is recommended for inclusion in the *Precautions* section of the PI: *"Epidemiological studies relating to Pandemrix in two countries (Sweden and Finland) have indicated a 6 to 13-fold increased risk of narcolepsy with or without cataplexy in vaccinated as compared with unvaccinated children/adolescents. This risk increase has not been found in adults older than 20 years."*

The results of Studies 009, 010 and 023 may be included in the *Clinical Trials* section of the PI. The CMI leaflet should be updated to reflect the recommended changes to the PI.

The advice from ACPM is requested as to whether these proposed actions are appropriate.

Response from Sponsor

Summary

The sponsor agrees to accept the TGA Delegate's recommendation to omit paediatric dosing information and to include further clarification statements to dosing recommendation in the age group below 20 years of age.

A copy of the revised RMP incorporating relevant risk minimisation activities relating to the narcolepsy is available and will be provided to the TGA OPR if required prior to approval.

The sponsor also agrees that in the event of a pandemic in Australia, an Australian specific annex will be developed to incorporate specific pharmacovigilance activities negotiated and agreed with the agency.

Response to questions in the Delegate's overview

Delegate's question: In view of the increased risk of narcolepsy associated with the use of Pandemrix H1N1 vaccine in people under the age of 20 and the availability of other influenza vaccine against the 2009 H1N1viral strain, the benefits and risks balance is not considered favourable for the use of Pandemrix H1N1vaccine in children and adolescents. The sponsor's request to include dosing schedule for children and adolescent (6 months to 17 years) is therefore not recommended.

Sponsor's response: The sponsor acknowledged TGA's comment on the increased risk of narcolepsy as indicated by data from Finland and Sweden. The sponsor has also reviewed newly reported data from Ireland, which can be found in the report "Investigation of an increase in the incidence of narcolepsy in children and adolescents in 2009 and 2010" available on <http://www.dohc.ie/publications/pdf/Final_Report_of_National_Narcolepsy_Study_Steering_Committee.pdf?direct=1>; the related press release dated 19 April 2012 can be found on <http://www.dohc.ie/press/releases/2012/20120419.html>. The sponsor is currently consolidating its position which will be shared with EMA, TGA and other regulatory authorities by 11 May 2012.

Meanwhile, the sponsor will implement in the PI the changes requested by TGA (details of these are beyond the scope of this AusPAR).

The sponsor has committed to the EMA to conduct additional studies to investigate the relationship between narcolepsy and Pandemrix vaccination. A retrospective cohort study is currently ongoing in Quebec, Canada, where Arepanrix, a GlaxoSmithKline Biologicals H1N1 vaccine similar to Pandemrix, had been widely used during the 2009-2010 pandemic. In addition, the sponsor is also assessing the feasibility and relevance of additional studies and the consolidated research proposals were discussed in early 2012 with the EMA (through a Scientific Advice procedure). A final plan will be proposed to the EMA in the coming months.

Delegate's question: In addition, it is recommended to modify the currently approved recommendation for use in 'adults aged 18 years and older' to 'individuals aged 20 years and older'. Alternatively, the PI should include the following statement: "In persons under 20 years of age, Pandemrix should only be used if the recommended annual seasonal trivalent influenza vaccine is not available and if immunisation against (H1N1)v is considered necessary."

Sponsor's response: The sponsor agrees to modify the currently approved recommendation for use with the second option recommended by the Delegate, that is, the PI should include the following statement: "In persons under 20 years of age, Pandemrix should only be used if the recommended annual seasonal trivalent influenza vaccine is not available and if immunisation against (H1N1) is considered necessary."

The sponsor proposes to include the statement in the Dosage and Administration section.

Delegate's question: To address the increased risk of narcolepsy, the following text is recommended for inclusion in the Precautions section of the PI. "Epidemiological studies relating to Pandemrix in two countries (Sweden and Finland) have indicated a 6 to l3-fold increased risk of narcolepsy with or without cataplexy in vaccinated as compared with unvaccinated children/adolescents. This risk increase has not been found in adults older than 20 years."

Sponsor's response: The sponsor agrees to include the recommended statement in the Precautions section of the PI. However, in view of the new data received from Ireland, an updated statement is proposed where "in two countries (Sweden and Finland)" is replaced by "in some EU countries". The text proposed for inclusion is provided[3].

Delegate's question: The results of Studies 009, 010 and 023 may be included in the Clinical Trials section of the PI. The CMI leaflet should be updated to reflect the recommended changes to the PI.

Sponsor's response: The inclusion of the results of Studies 009, 010 and 023 is in line with the sponsor's proposal, that is, to include the immune response in the Clinical Trials section, and the adverse reactions in the Clinical Trial Experience subsection of the Adverse Reactions section.

Risk management plan

The sponsor notes the comments from the OPR relating to the RMP and would like to provide the following clarifications.

Provision of a revised RMP which addresses the safety signal relating to narcolepsy: The sponsor provided a commitment to amend the RMP consistent with the TGA recommendation, however given a final version was not available at the time of submission committed to submitting the revision on approval. A further revision, version

[3] Note that details of discussions between the sponsor and TGA concerning specific PI statements are beyond the scope of this AusPAR. See the PI at Attachment 1 of this document for finally approved PI statements.

11, was finalised in alignment with the PSUR schedule and is now available for review by the TGA on request.

Sections of the RMP which clearly outline the risk minimization activities proposed for Pandemrix H1N1 are provided as an Attachment to the sponsor's response (these are not included in this AusPAR).

An Australian specific RMP annex has not been developed at present. The sponsor was however able to demonstrate *via* the pharmacovigilance activities undertaken during the 2009-2010 pandemic that it was capable of addressing the activities suggested by the TGA in the event of a pandemic, that is:

- RMP modified to address recommendations of the CHMP in pandemic situation
- Simplified PSURs were supplied to countries in which the product was supplied
- A PASS initiated in the UK and Sweden

It is understood and agreed that in the event of a pandemic in Australia, the sponsor will be required to submit and obtain approval for an AU specific annex which addresses specific criteria set out by the agency (beyond that already proposed by the sponsor).

Conclusion

The sponsor has agreed to the Delegate's recommendations to omit dosing recommendations for children aged 6 months to 17 years of age.

The sponsor also agrees to include clarification statements relating to use in adults between 18–20 years of age, given the identified potential risk of narcolepsy in this population.

The dosing recommendations have been amended (see *Outcome,* below, for finally approved *Dosage and administration* section).

Other comments in relation to recommended revisions to the PI are beyond the scope of this AusPAR.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered this product to have an overall negative benefit-risk profile for the proposed inclusion of a dosing schedule for children and adolescents aged 6 months to 17 years in the PI.

In making this recommendation the ACPM noted the significant safety signals with narcolepsy in the under 20 year age group and in view of the existence of alternative products with positive benefit-risk profiles, the ACPM did not support use in the proposed population group nor in individuals aged 18 or 19 years.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the following changes to the *Dosage and Administration* section of the PI for Pandemrix H1N1 pandemic influenza vaccine:

> "*Individuals aged 20 years and older:*
>
> *One or two doses of 0.5ml.*"

Other amendments to the PI for were also approved (details of these are beyond the scope of this AusPAR).

Specific conditions applying to these therapeutic goods

The implementation in Australia of the PANDEMRIX H1N1 pandemic influenza vaccine split virion inactivated AS03 adjuvanted 0.5 mL dose RMP version 5, February 2010 included with this submission, and any subsequent revisions, as agreed with the TGA and its OPR (refer to OPR correspondence of 23 April 2012).

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au
Reference/Publication #