Minutes of the

Adverse Drug Reactions

Advisory Committee

309th meeting

18 July 2008

Medicine	Reaction; ADRU reviewer comment	ADRAC comment
[redacted]		
Gardasil	Anaphylactic reaction (12th report). Other reports of note describe: coeliac disease, deafness, dysarthria, dyskinesia, grand mal convulsion, headache, hemiparesis, hypoaesthesia, retinitis viral, visual disturbances. PI very scant	
[redacted]		

[redacted]

10.1.1 Final report of the NSW Health Human Papillomavirus (HPV) Vaccination Program Adverse Event Review Panel. Cases of anaphylaxis following HPV vaccination in NSW.

An interim copy of the above report was considered by ADRAC at the 306th (Feb 06) Meeting, when difficulties associated with the use of variable case definitions for anaphylaxis were also discussed. A final report from the Expert Review Panel had recently been issued; the recommendations from this report are reproduced below.

RECOMMENDATIONS

FOR PRACTICE IN NSW

1) That systematic follow up of any further reported cases of anaphylaxis following receipt of HPV vaccine in NSW continue in 2008.

2) That the findings of the Panel be provided to Adverse Drug Reactions Advisory Committee of the Therapeutic Goods Administration, the Australian Technical Advisory Group on Immunisation and the National Immunisation Committee.

3) That information provided to parents in the school-based HPV vaccination program should continue to include the small but real risk of anaphylactic reactions occurring.

4) That all immunisation providers in NSW should continue to be reminded to be prepared for the occurrence of anaphylaxis following immunisation and have appropriate protocols and

equipment available. All patients should be monitored for at least 15 minutes following immunisation, as per recommended practice in the Australian Immunisation Handbook.

5) That the report, or a version thereof, be published to communicate the findings of the investigation to the international medical and public health community. This should occur following consultation with the Australian Department of Health and Ageing and the TGA/ADRAC.

FOR CONSIDERATION NATIONALLY

6) That all Australian jurisdictions be requested to follow up cases reported as anaphylaxis, including any instances, whether diagnosed as anaphylaxis or not, where adrenaline is administered following HPV immunisation. That wherever possible, standardised survey instruments and allergy testing protocols are used for the investigation of cases.

7) That clear advice to assist in decision making regarding subsequent doses for those who develop a rash in 24 hours or less following HPV vaccination is formulated and disseminated to providers. Such advice should be developed in the context of data from the NSW investigation, as well as information from detailed case reviews in other jurisdictions and other relevant reports following HPV vaccination as reported to ADRAC. The Panel endorses the following draft statement to be considered by ATAG/NIC as forming the basis for such advice:

'Specialist advice should be sought before considering the administration of further doses of HPV vaccine following the occurrence of suspected anaphylaxis or an acute generalised cutaneous reaction within 6 hours of immunisation. A generalised cutaneous reaction is characterised by urticaria, erythema or angioedema affecting one or more areas that are non-contiguous with site of immunisation.'

ADRAC was requested to comment on the final report and recommendations from the Expert Panel, noting also the comments from [redacted] regarding the recommendations for implementation Nationally.

Recommendation

ADRAC endorsed the report from the NSW Health Human Papillomavirus (HPV) Vaccination Program Adverse Event Review Panel and its recommendations. ADRAC suggested mechanisms should be pursued to ensure the recommendations arising from the report were implemented on a National level. To assist this, the Committee suggested that parts of the recommendations, in particular points 6 and 7, should be included on the TGA website; at the least, the paragraph beginning '*specialist advice should be sought before considering …..*' should be included.

In more general discussions, the Committee suggested that information relating to the safety of vaccines, including information about safe administration, should routinely be posted and updated on the TGA website. [redacted] undertook to liaise with [redacted] to assist this process.

10.1.3 Reports of MS-like symptoms with Gardasil

This item was provided as a late paper for advice from the Committee

In the week prior to the current Meeting, the NSW Health Immunisation program notified ADRU of 4 new reports (all originating from the same neurologist) describing multiple sclerosis-like symptoms in association with Gardasil. In addition, further information had been received for a previously submitted report (from the sponsor) describing similar symptoms.

The five cases range in age from 16-25 years old and presentations occurred 1-21 days following the 2nd (n=3) or 3rd (n=2) doses of Gardasil. Complete or near complete clinical recovery was observed in all patients following the administration of intravenous methylprednisolone. The following summary of these cases was presented:

Report 236306 (further information on a previously reported case)

This report describes a 21 year old female.
1st dose Gardasil 9 August 07 (batch J1022)
2nd dose Gardasil 30 October 07 (JI599)

Prior to vaccination: Patient experienced left optic neuritis. (1st presentation at neurologist was June 07; MRI scan also detected brain lesions – multiple, typical MS distribution)

Onset date 31 October 07- 24 hours post vaccination the patient developed symptoms of an incomplete transverse myelitis, paraesthesia of the left thumb and index finger, spreading to left hand and then right hand and 8 days later experienced recurrent left optic neuritis. MRI scan showed dramatic increase in burden of cerebral disease. A progress MRI scan in May 2008 showed marked improvement.
Diagnosis at presentation: clinically definite multiple sclerosis.
Past medical history of right hemifacial spasm throughout childhood.
Concomitant medicines were Estelle (cyproterone acetate and ethinyloestradiol).

Report 242796

This report describes a 25 year old female.
1st dose Gardasil 6 August 07 (J1022)
2nd dose Gardasil 1 November 07 (J2299)

Onset date 17 November 07 – 16 days post vaccination the patient experienced general lethargy, dysarthria and weakness in right limbs (right sided hemiplegia). Symptoms began to resolve within four hours of initial onset but residual impairment of fine hand motor skills persisted for 8 weeks. Brain lesion (left parietal cortical/subcortical) revealed on MRI scan. Four months after initial presentation the patient developed right leg paraesthesia and new brain lesion on MR scan.
Diagnosis at presentation: clinically isolated syndrome.

Report 242793

This report describes a 16 year old female.
1st dose Gardasil 2 May 07 (J0798)
2nd dose Gardasil 13 June 07 (J0800)
3rd dose Gardasil 19 September 07 (J2300)

After 1st dose patient experienced dizziness
After 2nd dose patient had headaches and concerned about memory impairment
A few days after the 3rd dose, the patient got up during the night and lost control of her legs and collapsed. The next morning she had recovered. Approximately 3 weeks after 3rd dose she developed right hand weakness and right hand clumsiness. Examination revealed marked pseudoathetosis of the right hand but no other abnormality. MRI scans of the brain and spine showed lesions. Repeat imaging at four months after initial presentation showed no changes in imaging of lesions.
Diagnosis at presentation: clinically isolated syndrome.
Was given IV methylprednisolone to assist recovery.

Report 242785

This report described a 16 year old female.
1st dose Gardasil 27 August 07 (J1022)
2nd dose Gardasil 25 October 07(J2299)
3rd dose Gardasil 18 February 08 (J2895)

Onset date 20 February 08 – 2 days post vaccination with 3rd dose patient developed headache then 2 days later developed spinal sensory syndrome and paraesthesia. Referred to neurologist who identified incomplete transverse myelitis and particularly aggressive multiple lesions. Four years prior to event the patient described vague episode of paraesthesia.
Diagnosis at presentation: clinically definite multiple sclerosis.

Report 242789

This report describes a 16 year old female.
1st dose Gardasil was 10 May 07 (J0798)
2nd dose Gardasil was 6 September 07(JO799)
3rd dose Gardasil (unknown)

Onset date 12 September 07- 6 days post vaccination the patient developed left leg weakness - incomplete transverse myelitis, over next few weeks - nausea, vomiting, facial numbness and diplopia.
Diagnosis at presentation: clinically definite multiple sclerosis.

Additional case

In addition to the 5 cases described above, TGA was recently notified of a separate report of a North American patient who developed MS like symptoms while travelling in Australia, 2 weeks after receiving HPV vaccine.

Previous reviews of neurological reactions with Gardasil

In view of the 6 cases, the sponsor had been contacted and requested to expedite the release of the 4th Periodic Safety Update Report which contains details of worldwide neurological ADRs. This was expected to be available for review at the following ADRAC Meeting. According to a previous PSUR review (covering the period 1 Jun 07 to 30 Nov 07), 54 cases of possible autoimmune disorders with Gardasil have been reported world-wide, including 7 cases of MS (6 from the USA 1 (of MS relapse) from Australia).

The most recent comprehensive review of all neurological ADRs with Gardasil by ADRAC was done at the 302nd (Aug 07) Meeting, when the Committee concluded *"At this stage it was not clear if there was an association between HPV vaccine and neurological reactions but this should be monitored closely."*

Product Information

The Australian PI for Gardasil (version dated March 08) mentions the following under *Post-Marketing reports*: "Nervous system disorders: dizziness, Guillain-Barré syndrome, headache, syncope."

ADRAC discussion

The Committee considered whether there is a plausible association between Gardasil and the MS-like symptoms described in the 6 reports; and whether further investigation and/or regulatory action was warranted regarding the possible neurological effects of HPV vaccine.

A Member recalled two additional neurological cases of concern in association with HPV vaccine: report 235453 (reviewed at the 306th Meeting), described acute disseminated encephalomyelitis 3 months after a second dose (4 months after the first dose) of HPV vaccine in a 16 year old girl. Report 237812 (reviewed at the 307th Meeting) described multiple sclerosis and optic neuritis in a 16 year old female 3 months after her first (4 months after the second) dose of Gardasil.

Members agreed the reports of MS in HPV-vaccinated females were of great concern and action should be taken to quickly establish if there is a vaccine-associated link. While there is a background rate of MS in females of various age groups, it was not yet clear how these rates compared with rates in HPV vaccinated females. The CNS lesions described in some of the cases are not typical of vaccine-associated neurological lesions, and therefore it was difficult to draw conclusions about causality on the basis of pathology. However, neurological reactions have been associated with other vaccines and there are plausible underlying mechanisms.

ADRAC considered that while an association between MS and HPV vaccine is plausible, it was not proven on the basis of reports reviewed to date. The Committee recommended that immediate action to more actively monitor cases of MS and other neurological reactions in HPV-vaccinated females could be taken by using existing vaccine safety monitoring programs and relevant specialist networks.

A Member undertook to liaise with the Australian Paediatric Surveillance Unit (APSU), which is established to "facilitate active surveillance of uncommon childhood diseases, complications of common diseases or adverse effects of treatment" and request that MS and related neurological disorders be included on the list of monitored disorders in all children regardless of vaccination status. To capture cases in older patients, another Member undertook to liaise with Australian

neurologists and request that they consider the possibility of a vaccine-related cause in female patients presenting with MS or relevant (defined) neurological symptoms.

The Committee recommended that neurological reactions in HPV vaccinated females should be actively monitored, in the first instance by utilising existing mechanism such as the Australian Paediatric Surveillance Unit and Australian neurologists' networks. [redacted] and [redacted] agreed to assist with this work.

[redacted]

HPV vaccine reports:

82 of the vaccine reports described reactions to HPV vaccine when given as a single vaccine. The reports were received from NSW (28), VIC (20), QLD (10), SA (6), WA (9), ACT (3), NT (5), TAS (1). Copies of all reports in association with HPV vaccine received from 13 Apr to 1 Jun 08 were provided to the Committee.

Events

The number of reports received in association with the majority of the vaccines is shown below:

Vaccine	No. reports	Vaccine	No. reports
[redacted]			
		Human papilloma virus (Gardasil)	93

Anaphylaxis (3reports)		
[redacted]		
240965	HPV	Six days after her first dose of Gardasil, a 12 year old developed an urticarial rash on her arms, legs, back, chest, neck and face, facial swelling and chest tightness. She was treated with promethazine and recovered.

Seizures/convulsions (11 reports)		
Report number	**Vaccine/s**	**Patient**
240044	HPV	6 days after her 2nd Gardasil dose, a 12 year old female

Seizures/convulsions (11 reports)		
		with history of recurrent febrile seizures had a shaking episode and painful arm; later she lost consciousness, and had palpitations, associated headache, fever, vomiting and visual changes. She was referred to a specialist
[redacted]		
240280	HPV	Report from sponsor of a nervous 20 year old female who was immunised while lying down and experienced a tonic-clonic seizure immediately after the injection.
[redacted]		
240960	HPV	A 24 year old female with history of epilepsy (but not on any medications) showed loss of consciousness and generalised seizures (for 20 sec) immediately following the vaccine immediately. She recovered without treatment within 1 hour.
[redacted]		

[redacted]

GBS (1 report) and other serious reactions in SOC 'nervous system disorder'		
Report number	**Vaccine/s**	**Reaction terms**
[redacted]		
241310	[redacted], Gardasil	Hypoaesthesia, dyskinesia, vomiting, dizziness, muscle twitching, somnolence

[redacted]

Extensive limb swelling (67 reports) *onset time is in days; 0 indicates reaction occurred on day of vaccination					
Case Number	**Patient Age**	**Patient Sex**	**Outcome Description**	**Trade Name Description**	***Onset Time**
[redacted]					
240085	45	F	Unknown	Gardasil	

Extensive limb swelling (67 reports)
***onset time is in days; 0 indicates reaction occurred on day of vaccination**

[redacted]

240992	14	F	Recovered	Gardasil	1

[redacted]

Rash, urticaria or pruritus (71 reports)
Note: An onset time of 0 means the reactions occurred on the day of vaccination. NS = not stated.

Case Number	Patient Age	Patient Sex	Outcome Description	Trade Name Description	Onset Time
239885	12	F	Recovered	Gardasil	0
239891	15	F	Recovered	Gardasil	0

[redacted]

240037	15	F	Recovered	Gardasil	0

[redacted]

Rash, urticaria or pruritus (71 reports) Note: An onset time of 0 means the reactions occurred on the day of vaccination. NS = not stated.					
Case Number	**Patient Age**	**Patient Sex**	**Outcome Description**	**Trade Name Description**	**Onset Time**
[redacted]					
240042	12	F	Recovered	Gardasil	0
[redacted]					
240142	14	F	Recovered	Gardasil	0
240151	13	F	Recovered	Gardasil	0
[redacted]					
240337	15	F	Recovered	Gardasil	NS
240361	24	F	Recovered	Gardasil	3
240510	21	F	Unknown	Gardasil	3
[redacted]					
240716	15	F	Recovered	[redacted] Gardasil	0
240717	12	F	Recovered	Gardasil	0
240718	14	F	Unknown	Gardasil	0
240719	??	F	Unknown	Gardasil	0
240731	14	F	Recovered	Gardasil	1
240740	14	F	Recovered	Gardasil	0
240745	12	F	Recovered	Gardasil, [redacted]	1
240748	15	F	Recovered	Gardasil	5
240755	19	F	Recovered	Gardasil	1
[redacted]					

Rash, urticaria or pruritus (71 reports)

Note: An onset time of 0 means the reactions occurred on the day of vaccination. NS = not stated.

[redacted]

	240793	12	F	Recovered	Gardasil	NS	
[redacted]						
	240798	26	F	Recovered	Gardasil	1	
[redacted]						
	240927	13	F	Recovered	Gardasil	0	
	240933	16	F	Recovered	Gardasil	2	
[redacted]						
	240941	14	F	Recovered	Gardasil	0	
[redacted]						
	240973	13	F	Recovered	Gardasil	1	
[redacted]						
	240984	0	F	Not yet recovered	Gardasil	0	
[redacted]						
	241242	15	F	Not yet recovered	Gardasil	0	
[redacted]						
	241301	14	F	Recovered	Gardasil	1	

[redacted]