Minutes of the

Adverse Drug Reactions

Advisory Committee

302nd Meeting

10 August 2007

[redacted]

8 Summary of reports for review

The line listing of reports lodged in the period covered by this Meeting (16 May – 30 June 2007) with proportional reporting ratios was provided. The following associations were highlighted at the Meeting:

Medicine	Adverse reaction	Reports in database (sole suspected)	Comment
[redacted]			
Gardasil (HPV vaccine)	various		See item 10.1.2
[redacted]			

10 Vaccines

[redacted]

10.1.2 Adverse events to human papilloma virus vaccine (Gardasil)

Background

Gardasil (quadrivalent human papilloma virus vaccine) was registered on 24 July 2006. From April 2007 Gardasil has been available to girls *via* a schools-based vaccination campaign and this was extended to women aged to 26 years from July 2007. Conditions of registration relevant to longer term assessment of the safety of Gardasil include submission of:

- the final Clinical Study Reports for Protocols 013 and 015 when completed.
- reports of long-term follow-up of subjects enrolled in Protocol 015 from the cancer registries in four countries in the Nordic Region (Sweden, Norway, Iceland, and Denmark).
- data concerning duration of immunity from the extension of Protocol 018-06 and long term safety in Protocol 018-05.
- annual reports and a final summary report of the U.S. pregnancy registry that [the sponsor] will establish.

Protocols 005, 007, 013 and 015 supported efficacy of Gardasil in the prevention of cervical disease. Together these studies randomised 20,887 women aged 16 to 26 years.

To early July 2007, the NSW Health Department had recently received 47 cases of ADRs to Gardasil, including several cases of suspected anaphylaxis, and had requested the TGA urgently review safety and quality issues regarding this vaccine. An out-of-session Meeting of the ADRAC by teleconference was convened on July 4th 2007 to discuss these concerns. On the basis of reports reviewed at that Meeting, ADRAC made several recommendations to enhance the safe use of Gardasil. There was no immediate requirement to alert the public to safety issues with this vaccine.

Minutes from the ADRAC teleconference on Gardasil, held 4 July 2007

ADRAC reviewed the draft Minutes from the ADRAC teleconference and requested they be ratified subject to the following amendments:

- Page 3, paragraph 7: amend this to read:

"Members commented on the difficulty of interpreting descriptions such as 'difficulty breathing', as this was a subjective rather than an objective phrase. It was noted that the girl was hospitalised, treated with adrenaline and recovered."

- Page 4, paragraph 5: amend the first part to read:

"Members suggested the description of the skin manifestation (mottled face to waist) would be consistent with generalised erythema. ADRAC noted the term 'cyanosed' was mentioned in the report, although the absence of stridor was specifically recorded."

- Page 5, paragraph 7: amend the first part to read:

"ADRAC noted that anaphylaxis is a rare event associated with most vaccines, with an incidence ranging from 1 in 100,000 to 1 in 1, 000,000 doses depending on the vaccine."

- Include the following reference to support the above statement:

Bohlke K *et al.* Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics* 2003; 112; 815-820.

At the teleconference, ADRAC requested the review of ADRs with HPV vaccine be kept on the agenda as a standing item until further notice. This first review provided a comprehensive summary of the issues and an overview of reports to ADRAC.

ADRAC data

To 17 July 2007 the TGA had received 224 ADR reports describing 639 reactions. These reports include 47 cases from NSW that were discussed at the out-of-session Meeting of ADRAC by teleconference. To date, there were no deaths related to Gardasil. The most frequent reactions were dizziness (54), nausea (45) and headache (44). Gardasil was the sole suspected drug in 218 of the 224 reports. The following were reactions of interest:

Reaction	No reports	Sole suspected
Syncope/vasovagal	25	24
Facial palsy	1	1
Dysarthria	3	3
Paralysis	1	1
Hypoaesthesia	14	14
Paraesthesia	11	11
Tonic/clonic movements	1	1

An initial cluster of 5 reports of syncope/vasovagal syncope originated from Vic but in the 3 weeks to 17 July a further 13 reports of syncope were received and the PI was updated to include information on syncope.

One case of particular interest was described in report s22 This involved a 16 year old girl who fainted 30 min after vaccination and was reported to continued to faint without warning thereafter, for a total of 12 times in 13 days. She complained of nausea, blurred vision, and mild twitching prior to fainting. The patient was referred to a GP and cardiologist but there were no notable findings in examinations of blood biochemistry or cardiac function (ECHO and Holter monitoring).

No seizure activity was detected and there were no pre-, no post-ictal symptoms. The girl was on no drugs and the GP diagnosis was simple faints with secondary gain. She was referred for neurological opinion and MRI scan. **Members agreed this was a puzzling case and suggested attempts should be made to obtain further information as it became available.**

The case of facial palsy occurred in a 15 yr old girl who 2 days post vaccination developed "swollen glands" on the opposite side to the vaccination site and her right eye became red and itchy. 5 days after vaccination the right side of her face drooped. Bell's palsy was suspected. She had not recovered when the report was made 2 weeks after vaccination. Two other cases suspected by the reporters to be possible Bell's palsy (s22 and s22) were discussed by ADRAC at the teleconference on 4 July. ADRAC was not convinced that either case was in fact Bell's palsy.

There were 2 reports of neurological ADRs that warranted further review. The first (s22) involved a 16 year old girl who developed shooting pain at her injection site 5 days after vaccination. This progressed to lack of movement. She was hospitalised with paralysis of her left arm. Her provisional diagnosis was complex regional pain syndrome. MRI of brain and nerve conduction studies was reported as normal. **Members requested attempts should be made to obtain further information for this case as it became available.**

The second event (report s22 / s22 / s22 concerned a 17 year girl who following a school-based vaccination had lunch and then "collapsed". She was taken to hospital where she was noted to have "ascending neuropathy" with weakness in her limbs and facial muscles and aphasia. She was admitted to hospital. CT and EEG were normal. Her symptoms resolved within 48 hours and her discharge summary noted that no organic cause was found for her symptoms.

A case (s22) that included a description stating hemiparesis was reported for a 16 yr old girl with a history of laminectomy for "slipped disc" in 2001 and with a brother who has spastic parapesis. She developed numbness at the site of injection on the afternoon of the day she received her injection of Gardasil. The numbness increased over the next 2 days and on day 5 after the injection she was unable to move her left arm and leg. She also had numbness in her throat and pain on the left side of her neck. She was hospitalised and it was stated that her symptoms were resolving 6 days after the vaccination. No diagnosis was given by the reporter. Members agreed this was a puzzling case that did not fit criteria for neurological conditions such as transverse myelitis that have been reported with other vaccines. Members considered the reaction may have been a conversion-type event, but more information was required to allow a better understanding of this case. **Members requested attempts be made to obtain further information for case** s22

Of the 11 episodes of paraesthesia the event occurred as part of an early onset post vaccination reaction (immediately or within 24 hours) with either dizziness and nausea or local pain and paraesthesia. The 3 episodes of dysarthria occurred immediately post vaccination in association with vasovagal type symptoms. One of these girls was reported to have had a similar reaction after MenC vaccination (ADR report s22).

There were 3 cases initially considered to be epilepsy possibly caused by Gardasil, though on review these cases were recoded. One was the consumer report associated with a series of syncopal episodes discussed above. Another was reported in a 16 yr old girl with microcephaly and slight developmental delay. She was reported to have fainted then had a convulsion with urinary incontinence 15 minutes post vaccination. She was seen in hospital and discharged. It is not known if she had a history of epilepsy or whether she was on any medication. The third case was another talk-back radio report of a mother who stated that her daughter was vaccinated with Gardasil and "got sick" 9 days later, and was noted to have had a convulsion and fractured 2 vertebrae. The

mother had said her daughter had been diagnosed with juvenile epilepsy and that the hospital did not think this was related to the vaccination but she disagreed.

There were 14 reports of hypoaesthesia. One of these was also diagnosed as a conversion reaction. This occurred immediately post vaccination in a 13 yr old girl who developed numbness, weakness and hypoaesthesia in her right leg. Another girl was also reported to have had hallucinations post vaccination in association with hypoaesthesia. She recovered. There was no information on the timing of these events relative to vaccination.

Anaphylaxis reports to ADRAC

In late June/early July 2007 the NSW Chief Medical Officer alerted the Department of Health and Ageing to 47 reports of adverse reactions to Gardasil, experienced by school girls taking part in the HPV immunisation program. These reports were received from various health professionals around NSW and were reviewed by a NSW Government Expert Panel. The Panel was particularly concerned about 7 reports judged to be anaphylaxis. The NSW Health Department subsequently sought advice from the Department of Health and Ageing regarding any requirements for action or review. TGA input was sought as part of the Federal Government's action on this matter. An out of session ADRAC Meeting to discuss this issue was held on 4 July.

On the basis of reports reviewed at this Meeting, ADRAC considered there was no immediate requirement to alert the public to safety issues with Gardasil vaccine. The Committee recommended investigations should continue to determine if there is a NSW-specific safety issue related to Gardasil. Product literature intended for Gardasil prescribers and consumers should be reviewed to ensure it adequately describes the risks and requirements for monitoring and management of symptoms. The sponsor should write to GPs advising of changes to the PI, and reminding them to maintain vigilance and monitor patients after vaccination. Information on safe immunisation practices should be included with this correspondence. The Government should ensure that adequate post-market programs are in place to monitor the safety of HPV vaccine.

Update on actions taken since the teleconference:

To date, no notable findings have been shown in sample tests of Gardasil (including batches used in NSW) by TGA Laboratories. On July 19th, a teleconference was held between representatives of the sponsor of Gardasil, the Delegate for Gardasil and staff from ADRU, to discuss ADRAC deliberations regarding this issue. The sponsor accepted ADRAC's recommendations and undertook to review its product literature on Gardasil, including the patient/guardian consent information, to ensure potential for hypersensitivity reactions are highlighted. Hypersensitivity to yeast will be included as a contraindication. The sponsor will also be issuing to prescribers general information on safe immunisation practices, and will review the incidence of ADRs to Gardasil in the context of rates of ADRs with vaccines in comparable mass-vaccination programs. The most recent PI and CMI documents for Gardasil were provided.

A review of the Gardasil PSUR covering the period 1 June to 30 November 2006 has since been completed. No media statements from NSW have been released to date.

US ADR reports with Gardasil

As part of an FoI request in the USA a group called "Judicial Watch" gained access to the US Vaccine Adverse Event Reporting System (VAERS) data. A detailed review of this information was provided to the Committee. However, it was noted that ADRs to HPV vaccine in the US are not entirely relevant to Australia because in the US, HPV vaccine has often been co-administered with other vaccines, including Menactra, a quadrivalent conjugated meningococcal vaccine

(serotypes A, C, Y and W) that is not registered in Australia, and influenza vaccines. A review of the US reports did not raise cause for concerns over and above that raised by Australian reports.

Literature

The following papers were noted for information:

- Paavonen, J *et al*. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. *Lancet* 2007; 369: 2161–2170
- [with editorial by Kahn and Burk: Papillomavirus vaccines in perspective].
- The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *NEJM* 2007; 356: 1915-1927.
- Garland S *et al*. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases *NEJM* 2007; 356: 1928-1943.
- Commentaries on HPV vaccine in the *NEJM* 2007; 356:
    - Sawaya G and Smith-McCune K. HPV vaccination — More answers, more questions
    - Baden L *et al*. Human papillomavirus vaccine — Opportunity and Challenge
    - Syrjänen S. Human papillomaviruses in head and neck carcinomas

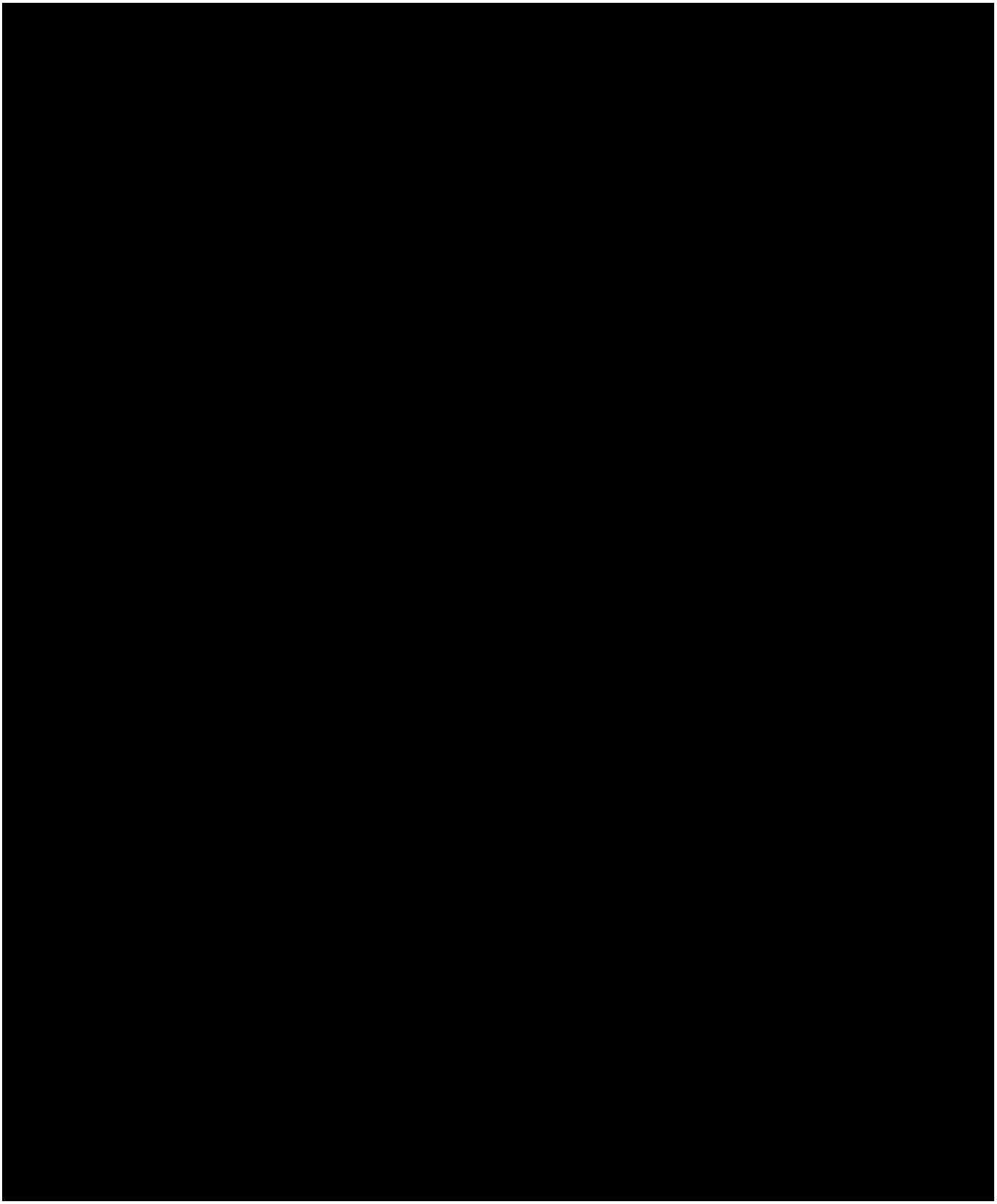
Discussion

Members noted there were three main groups of adverse reactions reported with Gardasil:

- Conversion-type reactions, with symptoms of fainting, dizziness, syncope and headache, sometimes associated with hypoaesthesia
- Allergic skin rashes – either non-specific or progressing to urticaria and angioedema
- Possible anaphylaxis

At this stage it was not clear if there was an association between HPV vaccine and neurological reactions but this should be monitored closely.

Members considered that current post-market safety monitoring strategies for Gardasil appeared to be adequate at this time. ADRAC noted plans by the sponsor to write to GPs advising of changes to the PI and reminding them to maintain vigilance and monitor patients after vaccination. Information on safe immunisation practices would be included with this correspondence. In NSW, the Government had established post-market programs to monitor the safety of HPV vaccine, and ADRAC would continue to actively monitor the safety of Gardasil *via* the spontaneous reporting system. No further action by the Committee was warranted at this time. **ADRAC requested adverse reactions with human papilloma virus vaccine should be kept as a standing item on the agenda until further notice.**



10.2 Vaccine reports

During the 6-week period from 16 May to 30 June 2007, about 345 reports of vaccine adverse reactions were lodged. This represents about 23% of the reports lodged for the period.

179 of the reports related to HPV vaccine (Gardasil), which have been discussed above. Virtually all of the Gardasil reports are for teenaged girls given the vaccine *via* school-based programs. The

number of reports received from each State or Territory are: VIC: 48; NSW: 47; QLD: 32; SA: 20; WA: 17; ACT: 9; NT: 4; TAS: 1; unknown: 2.

[redacted]

[redacted]

[redacted]

Case reports for all vaccines received in the period were provided to the Committee

Vaccine	No. reports	Inject. site reaction	Convulsion seizure	Fever/ pyrexia	Dyspnoea/ apnoea	HHE	Other notable reports/important reactions / comments
[redacted]							
Human papilloma virus (Gardasil)	179	28	s22 [redacted] ?	9	9		Neuropathy s22 [redacted] neurological symptom s22 [redacted] paralysis s22 [redacted] 12 rpts of hypoaesthesia, 2 rpts of anaphylaxis s22 [redacted]; 3 of hypersensitivity s22 [redacted]; 58 rpts of dizziness/syncope