Minutes of the

Adverse Drug Reactions

Advisory Committee

304th Meeting

2 November 2007

[redacted]

10 Vaccines

10.1 Vaccine issues and published articles

A Member with expertise in vaccines provided a summary of the pertinent findings in each of the following papers:

- Human Papillomavirus Vaccine. Letters to the Editor. *NEJM* 2007; 357: 1154-1156

[redacted]

10.2 Vaccine reports

During the 6-week period from 16 August to 30 September 2007, about 320 reports of vaccine adverse reactions were lodged. This represents about 21% of the reports lodged for the period. Reports with Gardasil accounted for the large excess of reports received in the current period when compared with the same period in 2006.

Reports of vaccines other than HPV vaccine

180 of the vaccine reports describe reactions to vaccines other than HPV vaccine given as a single vaccine. 80% of these related to children and 20% related to adults. About 70% of the reports were received from States, Territories or Local Government Shire Councils, 22% were received from health professionals, 8% were from sponsors and one was from a consumer.

17 of the 180 reports are in association with HPV vaccine administered at the same time as at least one other vaccine (hepatitis B vaccine in most cases). These reports are: s22 [redacted] s22 [redacted] s22 [redacted] The reactions described in these cases are consistent with those described for other vaccine reports or for other HPV vaccine reports, although s22 [redacted] (Gardasil and H-B Vax II) describes convulsion.

There were no vaccine-associated deaths. Details of reactions associated with individual vaccines are shown in the Table, below. All case reports for vaccines other than HPV vaccine were provided to the Committee.

HPV vaccine reports:

155 of the vaccine reports described reactions to HPV vaccine (this number includes the 17 cases where HPV vaccine was administered along with other vaccine/s). Gardasil was administered in all cases except one [redacted]),

The majority of the HPV vaccine reports were for girls aged 12 to 17 but 30 described women aged 18 to 25 years, one described a 27 year old female and one described a 77 year old female. The reports were received from SA (58), NSW (38), VIC (22), QLD (16), ACT (11), WA (5), TAS (4), NT (1) or from the sponsor with no State of origin given (2).

Almost all of the reports for HPV vaccine were received from State or Territory Government Departments, but a substantial number were received from non-Government health care professionals: 5 from NSW, 10 from VIC, 8 from QLD, one each from WA and NT, and all 4 of the Tasmanian reports. All reports in association with HPV vaccine were provided to the Committee.

Vaccine	No. reports	Inject. site reaction	Convulsion seizure	Fever/ pyrexia	Dyspnoea/ apnoea	HHE	Other notable reports/important reactions / comments
Human papilloma virus	155	24	s22 [redacted]	20	7		Anaphylaxis/hypersensitivity s22 [redacted]); circulatory collapse (s22 [redacted]); 43 x rash/urticaria/pruritus; 35 headache; 11 x syncope/ conversion disorder; 18 x paraesthesia or other aesthesia; 22 x nausea; see also reports s22 [redacted] (multiple allergy symptoms), s22 [redacted] (circulatory collapse); s22 [redacted] (Guillain Barre Syndrome).

[redacted]

10.2.1 Reactions with HPV vaccine

A Member provided an overview of reports with HPV vaccine received by the TGA. In general, the majority of the reports could be divided into 4 main groups: those describing various forms of skin rash at various times following vaccination; those describing syncopal/conversion-type events; those describing unusual neurological symptoms including various types of aesthesia; and those describing Level 1, 2 or 3 anaphylaxis according to the Brighton collaboration criteria.

Only two reports in the period covered by the current Meeting suggested possible anaphylaxis:

Report s22 [redacted]

This report from a Victorian hospital emergency department described a 16 year old female who experienced bronchospasm, distress, nausea, dyspepsia, dizziness, angioedema and urticaria 24-48 h after third-dose vaccination with Gardasil. The Committee agreed the symptoms were clearly consistent with Level 1 anaphylaxis. However, the association with Gardasil was uncertain because the reaction had occurred 24-48 h after the vaccine had been administered.

Reports s22 [redacted]

This was a complex case involving three reaction sequences in a 20 year old female. On the same day after administration of Gardasil, the patient experienced 'anaphylactic shock', with symptoms described as 'flushing', 'difficulty breathing', and 'feeling tightness in chest'. She was taken by ambulance to hospital and treated with adrenaline and hydrocortisone before being discharged 6 h after admission.

About 1 week later, she visited her doctor who reported muscle tightness at the injection site and the presence of enlarged glands on the side where the vaccine was administered (second and third sequences, respectively).

Members noted this patient had a history of hypersensitivity to multiple analgesic drugs. Although the report suggested the patient experienced 'anaphylactic shock', the description of the symptoms was not entirely consistent with this type of reaction. Members noted in particular the absence of cardiovascular symptoms and the lack of serious respiratory symptoms such as stridor. It was also unclear if the reported 'flushing' was associated with a skin rash or a vasomotor response.

Members were doubtful that the reaction in this case was one of anaphylaxis; at most the symptoms may be consistent with Level 3 of the Brighton Classification system, however, based on the information available at this time, the Committee agreed it was more appropriate not to categorise this case as one of anaphylaxis.

Members discussed the difficulties in interpreting ambiguous symptoms such as 'flushing' and 'difficulty breathing'; and also commented on the difficulties faced in assessing reports that state a patient experienced 'anaphylaxis' but no associated symptoms are mentioned. The Committee suggested reports of this type should be pursued to determine if more accurate and informative details are available from the reporter.

In addition to the above reports, the Committee noted there were about 40 reports that described rash, urticaria or pruritus in association with Gardasil, and one report [redacted]) describing Guillain Barre Syndrome (GBS). In the latter case, a 15 year old female who had received her second dose of Gardasil developed neurological symptoms 6 weeks following vaccination. ADRAC suggested the temporal relationship between vaccine administration and development of GBS was inconsistent

with a vaccine-associated event; Members agreed this case was unlikely to be associated with Gardasil.

Hypersensitivity with Gardasil to date

Members received a verbal report of all cases received to 30 October that have been assessed by the ADRU in association with Members of ADRAC as being anaphylaxis in association with Gardasil. In summary, 10 reports of this association had been received – 7 from NSW, 2 from WA and 1 from VIC. Four of these occurred after the first dose of Gardasil, 3 with 2nd dose; and no information on dose number was given in the other 3. All 10 cases were seen at hospital and 8 of the cases were given adrenaline. Seven cases were stated to have fully recovered at time of reporting. Details are shown below:

Report #	Brighton*	State	dose	Rx; outcome
s22	level 2	NSW	n/a	adrenaline; hospital; recovered
	level 3	NSW	1	hospital; recovered
	level 3	NSW	n/a	adrenaline; hospital; recovered
	level 2	NSW	1	adrenaline; hospital
	level 3	NSW	2	adrenaline; hospital; recovered
	level 2	WA	n/a	adrenaline; hospital; recovered
	level 2	NSW	2	adrenaline; hospital; recovered
	level 2	VIC	2	antihistamine; hospital
	level 2	NSW	1	adrenaline; hospital; recovered
	level 2	WA	1	adrenaline; hospital

*Classification according to the Brighton Collaboration case definition of anaphylaxis

There were also 39 reports that described urticaria but not anaphylaxis (10 from NSW, 9 from VIC, 6 from QLD, 5 from SA, 3 from the ACT, 2 from WA, 2 from TAS 1, from the NT, and 1 not stated). 26 of these was with the 1st dose; 5 with 2nd dose; 2 with 1st and 2nd doses; 1 with 3rd dose; and no dose information was provided in 5. 28 of the 39 cases stated the patient was recovering or fully recovered at time of reporting.

Members discussed general aspects concerning the on-going HPV vaccination program in Australia. It was noted that program administration and patient monitoring were extensive and thorough, and there was a very high rate of patient participation and follow-up. Specialist clinics established in various States were closely monitoring patient responses to the vaccine. Members suggested that ADRU, in association with ADRAC, was well-placed to assist in assessing safety aspects of the vaccine on a National basis.

[redacted]

14 Australian media

A collection of newspaper clippings on the following subjects was noted for information:

[redacted]

- HPV vaccine

[redacted]