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02 SEP 2016

[redacted]

Ref: H201603238

Dear [redacted]

Response to your request for official information

Thank you for your request of 6 August under the Official Information Act 1982 (The Act) seeking response to a number of questions relating to Gardasil vaccine.

Medsafe is part of the Ministry of Health and is responsible for administering the Medicines Act 1981 and it associated regulations in New Zealand.

1. Who reviewed the Nordic Cochrane Complaint in New Zealand?

The Nordic Cochrane Centre is an independent research and information centre that is part of the Cochrane Group, an international network of individuals and institutions committed to preparing systematic reviews of the effects of healthcare. On 25 May the Centre published a complaint to the European Medicines Agency (EMA) on their website (nordic.cochrane.org/research-highlights) .

Please note that this complaint was not directed at New Zealand authorities. The complaint centred around their opinion that there had been maladministration at the EMA. The legal and regulatory situation in New Zealand is different to Europe and so the complaint has no relevance in New Zealand.

Medsafe read the complaint and ascertained that although there is some discussion of the data considered by the EMA in its recent review of Gardasil safety, no new data was included in this complaint. Therefore no review of the complaint was deemed necessary. Medsafe had already reviewed the potential safety signal of Postural Orthostatic Tachycardia Syndrome (POTS) and Complex Regional Pain Syndrome (CRPS) which were the subjects of the recent EMA review. These potential safety signals were also taken to the Medicines Adverse Reactions Committee (MARC) for expert advice. The minutes of the meeting are available on Medsafe's website (www.medsafe.govt.nz/profs/adverse/Minutes164.htm).

The EMA has published its response to the Nordic Cochrane Centre in two parts www.ema.europa.eu/docs/en_GB/document_library/Other/2016/07/WC500210542.pdf

www.ema.europa.eu/docs/en_GB/document_library/Other/2016/07/WC500210543.pdf

Names have been withheld under section (9)(2)(g)(ii) to maintain the effective conduct of public affairs through the protection of employees from improper pressure or harassment.

2. *When was this review carried out and over what period of time?*

Not applicable

3. *What specific issues were reviewed?*

Not applicable

4. *How were these specific issues reviewed?*

Not applicable

5. *On what grounds was the conclusion reached, that current evidence does not support an association, between Gardasil and any particular adverse event?*

'Any particular adverse event' is taken to mean syndromes such as POTS and CRPS which have been described as potential safety signals with Gardasil. This issue was discussed by the MARC and the minutes published on the Medsafe website as described above.

6. *Which adverse events are you referring to?*

See response to question 5.

7. *What evidence do you have, or those who carried out this review, that demonstrates that there are NO safety issues with the HPV vaccine Gardasil?*

All medicines have side effects and all medicines attract safety concerns during their lifetime. The same is true for Gardasil. The side effects with at least a reasonable possible association with Gardasil are listed in the data sheet, published on the Medsafe website (Nordicwww.medsafe.govt.nz/profs/datasheet/DSForm.asp). POTS and CRPS have been raised as safety concerns with Gardasil, reviewed and dismissed. Should further scientific evidence become available these issues will be reviewed again. This is the normal process of pharmacovigilance. However, please note that further case reports will not change the current assessment, because a well conducted epidemiological study is required at this stage.

8. *How was it decided that there is no new evidence, that requires a reassessment?*

See response to question 1.

9. *What justification does the Minister of Health have, or anyone else from the Ministry of Health, for not believing that a highly regarded international group, such as the Nordic Cochrane Group, raising serious concerns, regarding the European Medicines Agency's evaluation of the Gardasil vaccine, is not a matter that they needed to follow up or investigate?*

Medsafe notes that the Nordic Cochrane Centre may be well regarded in the field of meta-analysis and systematic review. However the science of pharmacovigilance is not within their scope of expertise. As stated by the EMA in their response.

"EMA, therefore, is somewhat surprised that – different to your previous approach – you appear to now overestimate the value of studies that have important limitations such as lacking a comparator group."

Medsafe also note that the letter writers failed to outline their conflicts of interest. It is noted that the Danish Syncope Unit is in receipt of funding to study their proposed association between POTS and Gardasil, which constitutes a conflict of interest.

In addition the Nordic Cochrane Centre failed to identify the correct Julie Williams. As stated by the EMA.

"Regarding your comments on the PRAC Rapporteur Julie Williams, we would like to clarify that you are in error as you are referring to a totally different person of the same name.

The PRAC rapporteur Julie Williams is not a Professor of Neuropsychological Genetics at Cardiff University or the Chief Scientific Adviser for Wales as you claim and she did not co-author the article that you mentioned. The Wikipedia webpage you mention refers to a different person."

In addition to these questions, I presume by you stating that no new evidence was presented in the Nordic Cochrane Complaint, you are confirming that:

1. *You were aware of the use of the adjuvant amorphous aluminium hydroxyphosphate sulphate, as a placebo and in the Gardasil vaccine itself, at the same time, in the clinical trials. Is this correct and when were you aware of this fact?*

In December 2001, the pharmaceutical company made an application to Medsafe under section 30 of The Medicines Act 1981 to run a clinical trial for Gardasil in New Zealand. This application was to include a New Zealand arm in studies V501-012-00 and -013-00. The application was reviewed by the Health Research Council (HRC) committee: Standing Committee on Therapeutic Trials (SCOTT), as per the normal process. SCOTT gave approval for the trial(s) to proceed in New Zealand. The patient consent form for the trials stated that the placebo used in the trials contained 225 micrograms of aluminium. Gardasil trials are registered on the US clinical trials register, further details are provided on the website: https://clinicaltrials.gov/ct2/home.

2. *Could you explain why this was deemed acceptable, in view of the WHO Gold Standards for placebos to be used in new vaccine trials?This placebo was after all a 'new proprietary adjuvant' as well.*

This issue was addressed in the EMA response stating.

"Study 018 for Gardasil investigated almost 700 subjects using an inactive placebo. The study's primary objective was to evaluate the safety of Gardasil among 9- to 15- year-old boys and girls. This study allowed the comparison of Gardasil with a non-aluminium-containing placebo (all other studies compared the vaccine with aluminium containing placebo, as mentioned). Subjects were also evaluated for new medical conditions 1 year

post vaccination. The data from study 018 was compared with the safety of the antigens and adjuvant as evaluated in the rest of the clinical trials.

Overall there was no significant increase in the reactogenicity following Gardasil vaccination as compared to the non-aluminium containing placebo administration. Local pain, headache, nausea and pyrexia were the most common symptoms observed in both groups. The only major difference noted between aluminium containing placebo and placebo without aluminium was the rate of local pain which was less frequent after non-aluminium-containing placebo administration (45.4% in non-aluminium placebo vs. 75.4% in aluminium-placebo).

For both vaccines development, the use of Al(OH)3 (500μg) rather than a true placebo (inactive control) was found acceptable by the CHMP in order to maintain the double blinding of the studies and consequently the validity of data. The use of an active control as placebo (i.e. an unrelated vaccine) was found acceptable from an ethical perspective especially in trials involving children since it confers benefit to subjects randomised to the control group.

The approach taken for both vaccines was found by the CHMP as a reliable way to establish the safety profile of the vaccines at the time of authorisation."

3. *Could you provide the scientific evidence that demonstrates that AAHS is not neurotoxic?*

The scientific literature is publically available and can easily be accessed using PubMed (www.ncbi.nlm.nih.gov/pubmed/). Medsafe is unable to provide copies of papers due to copyright restrictions.

The EMA states "The safety of aluminium as adjuvant is considered well characterised based on data from clinical trials and decades of use with several antigens in different types of vaccines licensed worldwide. On the basis of the scientific assessments performed over the years by EMA and other experts such as from EFSA, FDA and WHO, the scientific evidence available to date continue to support the safe and effective use of aluminium adjuvants in vaccines."

4. *Could you explain why in the adverse outcomes data, AAHS placebo cohort data and Saline placebo cohort data, were 'combined' and reported as one column of data and then compared, with the Gardasil cohort adverse outcomes data? (The adverse events in the AAHS and Gardasil cohorts, were comparable, as evidenced in the clinical trials)*

I have assumed you are referring to tables 11 and 12 in the Gardasil data sheet. The data sheet remains the property of the pharmaceutical company. Data sheets are published on the Medsafe website for easy access by healthcare professionals. The acceptability of the data sheet is considered during the application for consent to distribute a medicine in New Zealand. The reports for the Gardasil application are published on the Medsafe website (www.medsafe.govt.nz/publications/OIA/Gardasil%20December%202015/Contents.asp).

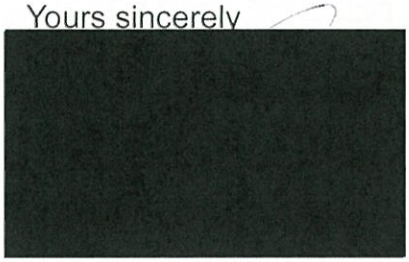
5. *Could you confirm that the non alum placebo, otherwise referred to in the Product Monograph, as the carrier solution, contained L-Histidine, Sodium Borate and Poly*

Sorbate 80? If not, what did the non alum/carrier solution contain as far as you were aware?

I have assumed you are referring to the Gardasil data sheet as there are no Product Monographs for medicines in New Zealand. The Data sheet states: "Both aluminum and non-aluminum containing placebos contained the same minor ingredients (0.78 mg of histidine and 50 mcg of polysorbate 80) as GARDASIL."

I trust this information fulfils your request. You have the right, under section 28 of the Act, to ask the Ombudsman to review my decision to withhold information under this request.

Yours sincerely



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