Svar modtaget fra EMA pr. mail den 8. februar 2016

Question 2: Comments on the Responsum by Dr Brinth

The Responsum document written by Dr Brinth and dated 15 December 2015 presents a detailed reply to the PRAC Assessment Report (AR) on the referral concerning complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) in young women given human papillomavirus (HPV) vaccines. However, it does not provide any new data or information in relation to the said HPV vaccine referral. Therefore, the conclusions in the PRAC AR and the interpretation/analysis supporting those conclusions are not affected.

More specifically, please note that Sections 2.1 to 2.3 of the Introduction of the Responsum document are background sections that do not provide any new data or information that is pertinent to the HPV vaccine referral.

Section 3 presents the work and approach of the Syncope Unit at Bispebjerg and Frederiksberg Hospital (Section 3.1) and also provides further information and some clarification of the chronology of the first two papers from Dr Brinth and her colleagues (Section 3.2).

Some of the comments made in this document suggest that there are several aspects of the PRAC discussion regarding the Brinth publications that appear to have been misunderstood; for example, case series methodology will always suffer from important limitations as it lacks a comparator group and also are known to be vulnerable to selection bias, regardless of whom conducts the analysis. The latter remains an issue with the Brinth and colleagues case series despite the efforts that they took to minimise this; another example is that Dr Brinth took as direct criticism of the work, the potential of misinterpretation of data due to the likelihood of recall bias, which is something innate to the used methods, and is partly driven by the patient awareness.

The document does highlight that there are possibly many more cases that have been referred to the Syncope Unit (the figure of 650 included in figure on page 16), but no further information on these cases and whether or not they occurred in HPV vaccinated individuals have been provided. However, the observed versus expected scenarios for Denmark suggested that the 650 figure included by Dr Brinth is within the range of expected scenarios. Furthermore, as both POTS, CRPS and Chronic fatigue syndrome (CFS) are issues that remain under close scrutiny and will be subject to updated observed versus expected analyses, any further cases reported to regulatory authorities or industry will be factored into future regulatory assessment and decision making.

The approach taken in this referral procedure by applying the observed versus expected analysis allowed the PRAC to use the most sensitive detection of a possible excess of the natural background rates and account for a range of possible under-reporting up to 99%.

Regarding Section 4 of the document provides Dr Brinth's, it comments on how it is alleged that the PRAC has misunderstood and, in some places, misinterpreted the Uppsala Monitoring Centre (UMC) report. We would like to note that what is included in the PRAC AR reflects the assessment of the PRAC and therefore the PRAC took into account the data from UMC accordingly.

In addition, Section 5 of the Responsum document highlights what is considered as an apparent discrepancy between what is included in the European public assessment report (EPAR) for Gardasil 9 and the PRAC AR with regards to cases of POTS and CRPS (3 cases of POTS and 1 of CRPS quoted in the EPAR but only 2 cases of POTS quoted in the PRAC AR). In this respect, we would like to clarify that the

one case difference in these figures is owing to that case being reported by the Danish authorities to the marketing authorisation holder (MAH) after the study was completed. The identity of this subject was not verified at the time of authorisation for Gardasil 9, and additional information had been requested. However, at the time of the HPV vaccines referral, the identity of this case was still not verified, and therefore the subject was not included among the cases.

Section 5 also highlights a potential misunderstanding of the nature of the Donegan and colleagues study and questions whether the results of this study that examined Cervarix can be applied to Gardasil. Overall, the concluding remarks in this Section 5 basically pose the same question as in the PRAC AR, i.e. the need for a broader look at fatigue-related conditions.

Regarding the comments in Section 5 on the Scientific Advisory Group (SAG) consultation, please note that the report of the SAG was part of the PRAC AR and made publicly available. In addition, the Mandate, Objectives and Rules of Procedure document of the SAG was followed as usual. This document is available in the EMA website together with other supportive documents (available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CHMP/people_listing_000116.jsp&mid=WC0b01ac058058f32e).

Moreover, we would like to point out that Eudravigilance data were assessed in this review, as stated in the PRAC AR, and the literature review was independently done by the assessing teams and the EMA, in addition to the ones submitted by the MAHs.

Likewise, Section 6 and Section 7 also do not provide new data or information. Section 6 discusses different hypotheses, and agrees that the overall data does not merit a different interpretation; and in Section 7, Dr Brinth reflects on the current situation regarding the HPV vaccines and the available data, suggesting further questions that may be of interest to the academic/medical community.

Question 3: SAG Confidentiality.

The obligations of SAG members regarding confidentiality are described in section 3 (Confidentiality undertaking) of the document 'Public Declaration of Interests and Confidentiality Undertaking', linked below:

http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2014/12/WC500178504.pdf

This document is signed by each individual SAG member prior to any SAG meeting.

Please note that the terms confidential information and confidential documents, to which confidentiality applies, are also clarified:

> *"**Confidential Information** means all information, facts, data and any other matters of which I acquire knowledge, either directly or indirectly, as a result of my EMA Activities."*
>
> *"**Confidential Documents** mean all drafts, preparatory information, documents and any other material, together with any information contained therein, to which I have access, either directly or indirectly, as a result of my participation in EMA Activities. Furthermore, any records or notes made by me relating to Confidential Information or Confidential Documents shall be treated as Confidential Documents."*

In addition, the document clarifies that:

"This undertaking shall not be limited in time, but shall not apply to any document or information that I can reasonably prove was known to me before the date of this undertaking or which becomes public knowledge other than as a result of a breach of any of the above undertakings."

Therefore the SAG attendees need to be careful not to reveal confidential information (including names of other attendees) and not to disclose confidential documents based on the definitions given above. As you are aware, the PRAC assessment report for the HPV vaccines referral has been published and it includes the full SAG responses to the PRAC questions.

Please also note what is mentioned in the **SAG Mandate, objectives and rules of procedure** document regarding confidentiality, which can be found publicly available here: http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CHMP/people_listing_000116.jsp&mid=WC0b01ac058058f32e, and in which it is further clarified:

"The Members of the SAG as well as observers and all experts shall be bound, even after the cessation of their duties, not to disclose any information, which, by its nature, must be covered by individual professional secrecy. The EMA Guidance on Confidentiality and Discretion applies. SAG members when participating in meetings or other fora on behalf of the Committee, shall ensure that the views expressed are those of the Committee. When they are participating not on behalf of the Committee, they shall make clear that the views expressed are their own."

The SAG Mandate, objectives and rules of procedure document is applicable to all SAGs and it is not solely applicable in the case of SAG-Vaccines (see link http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000102.jsp&mid=WC0b01ac058002d0ec).

Should you need further information, please do not hesitate to contact the EMA.