EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 February 2010
EMA/257008/2010
Evaluation of Medicines for Human Use

Variation Assessment Report

Invented name/Name: Celvapan
International non-proprietary name/Common name: pandemic influenza vaccine (H1N1) (whole virion, vero cell derived, inactivated) A/California/07/2009 (H1N1)v

Type II Variation: EMEA/H/C/000982/II/0012

Indication summary (as last approved):	Prophylaxis of pandemic influenza in an officially declared pandemic situation
Marketing Authorisation Holder:	Baxter AG

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

Based on reports received during the period of review and the strong causal relationship to CELVAPAN as well as continued adverse reaction reports for the events of anaphylactic reaction, hypersensitivity and paraesthesia, it was previously recommended in the Addendum to the Clinical Overview and Addendum to the Clinical Summary of Safety, both dated 02 December 2009, to include these terms into the SmPC.

In addition to continued reports for anaphylaxis, a second S-PSUR (covering 17 November 2009 through 14 December 2009, report dated 23 December 2009) identified new safety concerns including convulsions, pain in extremity and influenza-like symptoms. It is therefore recommended to include these terms in the SmPC, Section 4.8.

2. Clinical safety aspects

- **Influenza-like illness**

The MAH proposes to amend the SPC and add the term "influenza-like illness" (ILI) to section 4.8. ILI is also labelled for other pandemic and seasonal flu vaccines. The proposal is endorsed by CHMP.

- **Pain in extremity**

The most frequently reported unlisted adverse reaction in the 2nd sPSUR was pain in extremity (n=22). Therefore, the company proposed to label the term.
However it was unclear whether the pain in extremity is an injection site reaction or whether other limbs could be involved.

The MAH clarified that up to 11 January 2010 (data lock point of the 3rd S-PSUR) the MAH received 79 (47 serious, 32 non-serious) reports involving pain in extremity; thereof, 27 cases were reported for Celvapan and 52 for an unspecified H1N1 vaccine. Sixty-eight cases were reported in adults, 5 in children and in 6 cases the age is unknown. The MedDRA LLTs were:

- Pain in arm; Painful arm: n=46
- Aches and pains in legs; Pain of lower extremities: n=9
- Aching pain in hands, forearms and elbows; Painful hand: n=3
- Pain in extremity, Aching in limb: n=21

The vast majority of reports involve "pain in arm." In only 17 cases was painful arm specified as the injection site arm; in all other reports the injection site and/or the concerned arm were unknown. However, based on the latency (one day to two days) between vaccination and onset of pain reported for these cases, an injection site reaction radiating into the injected arm seems to be most likely.
The MAH proposed to further specify the term in the SPC as follows:
"MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS: Pain in extremity (in the majority of cases reported as pain in the injection site arm)."
The CHMP endorsed this proposal.

- **Convulsion**

In the 2nd sPSUR 4 reports that might be indicative for a possible convulsion have been described. Two reports meet the Brighton level 1 of diagnostic certainty. The remaining 2 reports were already diagnosed as convulsions by the physicians with no detailed description.

- The first case concerns a patient with unknown age and gender who most likely experienced immediately following Celvapan vaccination a convulsive syncope.
- The second case refers to a 41 year old woman who developed chills and fever and vertigo when walking following vaccination. She collapsed and experienced tonic convulsions. A herpes zoster was diagnosed, which might explain the symptoms.

- The third case refers to a 21 year old female patient with a medical history of epilepsy (seizure-free for two years) who experienced dizziness, pallor and convulsion on the vaccination day. Concomitant medication included lamotrigine.
- The fourth case refers to a 33 year old male patient with a medical history of epilepsy and mental disability who experienced a convulsion 24 hours after Celvapan vaccination.

In summary one case reflects most likely a convulsive syncope and one case most likely has an alternative cause (herpes zoster). Of some concern are the two cases of convulsions in patients with seizure disorders in a short temporal association with vaccination.

The company proposed to add the term "convulsion" to the SPC. This term apparently includes febrile and non-febrile seizures. In contrast to febrile seizures which are associated in particular with childhood vaccination, there is at present no evidence that vaccination can cause non-febrile seizures or can trigger the re-occurrence of seizure activity in patients with pre-existing seizure disorders.

The MAH was therefore requested to present a detailed cumulative review of all case reports of seizures in patients with a known history of seizure disorders following Celvapan administration.

The MAH clarified that a narrow SMQ query for convulsions (data lock point of the 3rd S-PSUR) revealed 9 reports (6 for Celvapan and 3 for an unspecified H1N1 vaccine).

Febrile convulsion:
2 reports in 1-year-old children (1 for Celvapan and 1 for the unspecified H1N1 vaccine). The events occurred with a reasonable temporal association to the vaccination and due to lack of any alternative aetiologies.

Additional cases of febrile convulsions are described in the overview of data from clinical trials below.

Non-febrile convulsion in patients with medical history of epilepsy:
3 reports (2 with Celvapan, 1 with unspecified H1N1 vaccine) concerning patients (aged 21 years to 56 years) with a medical history of epilepsy and concomitant antiepileptic treatment. In one of these cases, the patient had been seizure-free for 2 years prior to vaccination, suggesting good control of underlying epilepsy.

In the fourth case involving Celvapan, the 3-year old patient had a family history of epilepsy only. In those four cases, the latency between the vaccination and the occurrence of the event ranged between hours and 2 days. For one case an epileptic aura without convulsion that occurred on the vaccination date was reported. No further information with respect to severity and type of epilepsy, frequency of convulsions or compliance to antiepileptic treatment was provided.

Non-febrile convulsion in patients with no relevant medical history:
3 cases (2 with Celvapan, 1 with the unspecified H1N1 vaccine). In 2 cases the event occurred on the vaccination day and no alternative aetiologies were provided. In one case the convulsions occurred one day after vaccination and concomitant dermatological herpes zoster infection was diagnosed. However, CT of head and lumbar puncture did not show evidence for encephalitis due to endogenous reactivation of herpes zoster.

Upon request to provide an overview of the expected background incidence of fatal and non-fatal seizures in epileptic patients, based on available databases and medical literature, the MAH provided no background data and argued that due to the diversity of the clinical manifestations of epilepsy and lack of consensus on background incidence of seizures in epileptic patients, no valid background incidence can be provided.

The MAH was further requested to provide an analysis of the 'observed vs expected' incidence of non-fatal seizures in epileptic patients. In the absence of accurate exposure data, this analysis should incorporate appropriately justified assumptions/estimates on exposure

Baxter clarified that although observed to expected comparisons may provide insight regarding causal versus coincidental events, such comparisons are limited by a number of factors, including incomplete reporting/ascertainment, uncertain exposure data with potential to falsely dilute signals (where distribution data is used as a surrogate), lack of standard hazard windows, and lack of consensus on appropriate background rates for populations of interest. Of primary concern is the potential for false negative results in the comparison of a reporting rate to a background incidence rate to confirm a signal arising from qualitative data review.

Based on these limitations, the MAH, regarding the decision to add convulsions (febrile and nonfebrile) to the CCDS, has been relying on evidence from the medical review of individual case reports (qualitative assessment) rather than on the proposed observed vs expected analysis.

The MAH presented an overview of any relevant data from clinical trials of Celvapan (including any H5N1 studies) and stated that no reports concerning convulsions are available.

The clinical database size includes:

- H5N1 clinical trials: 3576 subjects (3116 between 18 and 59 years old, and 460 aged 60 years and above)
- Ongoing H1N1 clinical trials: adults > 18 years of age (406 subjects, all of whom have already received the second vaccination) and children and adolescents aged between 6 months and 17 years (101 subjects aged 9-17 years, 100 subjects aged 3-8 years, 100 subjects aged 6-12 months and 39 subjects aged 6-11 months; all except 3 subjects from the youngest age group have received the second vaccination)

- Ongoing observational study:

As of February 1, 2010, there have been 3000 subjects enrolled. Follow-up information from approximately 1100 subjects is presently available. 3 reports concerning convulsions have been received: Two reporting febrile convulsions, which occurred in children, and one reporting an epileptic seizure in an adult subject.

The febrile convulsions were reported in a 9-year-old child without a history of previous convulsions and in an approximately 3-year-old child with a history of prematurity and repeated febrile convulsions since February 2009. The interval between vaccination and onset of the adverse experience was 2 and 9 days, respectively. In both cases causality was assessed as possibly related by the investigator.

The epileptic seizure occurred in an approximately 50-year-old male with history of a haemorrhagic insult 2 years ago, who has suffered since then from dizziness and memory loss. After this epileptic seizure the subject was admitted to hospital, where a second epileptic seizure, followed by postictal amnesia, occurred. In addition, according to the subject, he has a history of an abnormal EEG; however, no epileptic seizures were reported in his medical history. The epileptic seizures occurred approximately one month after the Celvapan vaccination and causality was assessed as unlikely related by the investigator.

The MAH clarified that no incidences of “convulsions” were recorded in any of the H5N1 non-clinical toxicology studies.

Discussion:

The term “Convulsion” is already labelled in the section experience with interpandemic trivalent vaccines. The evidence for this is unknown.

The MAH proposes to label febrile and non-febrile convulsions on the basis of a few single case reports: 4 case reports with febrile convulsions (thereof 1 with unknown brand) and 8 case reports with non-febrile-convulsions (thereof 2 cases with unknown brand and one case with an un-plausible temporal relationship). 3/8 cases concerned patients with a history of epilepsy. For several cases relevant medical information is lacking. A single case assessment of the causal association between vaccination and the event is not possible.

There is biological evidence that childhood vaccination may be associated with febrile convulsion. However there is no biological evidence so far that non-febrile convulsions are linked to vaccination.

In the SPC guideline in section 4.8 it is stated that all adverse reactions from clinical trials, post-marketing studies or spontaneous reports attributed to the medicinal product with at least reasonable suspicion should be labelled. The MAH has not presented data in this respect. Labelling of non-febrile convulsion doesn’t appear to be justified from a scientific point of view.

Therefore CHMP concluded to include the term “febrile convulsions” into the SmPC.

3. Conclusion

On 18 February 2010 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.