14 April 2011
EMA/CHMP/283690/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Celvapan

pandemic influenza vaccine (H1N1) (whole virion, inactivated, prepared in cell culture)

Procedure No.: EMEA/H/C/000982/II/0017/G

Note

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

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1. Scientific discussion

1.1. Introduction

Celvapan is a Vero cell derived, monovalent, whole virion, inactivated H1N1v vaccine. The application for a marketing authorization for Celvapan was supported by a core dossier for pandemic influenza vaccine and the scientific development was based on the guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application (CPMP/VEG/4717/03) and the guideline on submission of marketing authorisation applications for pandemic influenza vaccines through the centralised procedure (CPMP/VEG/4986/03). The European Commission issued a Marketing Authorisation (MA) under exceptional circumstances for Celvapan (EU/1/08/506/001 containing a non circulating A(H5N1) strain) on 4 March 2009.

The strain change of the mock-up vaccine from H5N1 to H1N1v was approved on 06/10/2009 (EMEA/H/C/982/PU/02). Following the switch from pandemic to post pandemic phase the MA was modified as regards the conditions of authorisation from exceptional to non-exceptional authorisation and indication on 13/08/2010 (EMEA/H/C/982/SW/14). As a result the recommended indication now reads as follows: *Prophylaxis of influenza caused by A(H1N1) 2009 virus (see section 4.4 of the SmPC). Celvapan should be used in accordance with Official Guidance.*

The MAH submitted a revised product information on February 17, 2011 via a group of 5 type II variations. This variation application was filed following the assessment of the available data in accordance with follow-up measures and specific obligations defined below:

- SOB030: interim report of the pandemic observational safety study based on the first 3000 vaccinees;
- FUM038: Part B of the CSR of study 810705 (safety data from H5N1 prepandemic vaccine);
- FUM039: Part B Day 181 CSR of study 820902 (data on antibody persistence);
- FUM040: Part A Day43 report of study 820903 (SRH and MN results in infants and children aged 6 to 35 months);
- PSU043: first full PSUR assessment.

This procedure II-17/G aims at updating the product information to reflect immunogenicity and safety results available following conclusion of clinical trials in infants and children aged 6 to 35 months, data on antibody persistence in adults, safety information with Celvapan containing the A/H1N1/California/07/2009 influenza virus from observational studies and postmarketing experience and safety data from H5N1 studies.

The variations submitted in the group are the following:

Variation(s) requested		Type
C.I.4	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II
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Group of 5 type II variations (C.I.4) to update of sections 4.8 and 5.1 of the SmPC further to the evaluation of clinical follow-up measures (FUMs 30, 38, 39 & 40) and of the PSUR covering the period from 6 October 2009 to 30 September 2010 as requested by the CHMP. The section 4 of the PL has been updated accordingly. The MAH took the opportunity to correct mistakes in section 4.3 and 4.6 of the SmPC, to update the contact details for the local representatives in the PL in line with the latest QRD template, to delete the DDPS version number as per CHMP October 2010 request, and to update Annex II other conditions as requested by the CHMP.

1.2. Clinical aspects

Rationale for the proposed change

The changes proposed by the MAH in this group of variations have originated from the following studies requested via follow up measure as indicated:

1. SOB 30: Outcome in the reactogenicity evaluation set from the first 3000 vaccinees in the pandemic observational study ("A prospective non-interventional observational study to assess the safety of two vaccinations of a Vero cell derived, whole virus H1N1 pandemic influenza vaccine in subjects exposed to the vaccine through policies by governments or health authorities") lead to update of section 4.8 (H1N1). The report was previously submitted on 19 Apr 2010– and the Assessment Report of 25 May 2010 and outcome fax of 6 Jul 2010 are annexed to this report. Although the assessment report (AR) of 25 May concluded that the analysis of the MAH was endorsed and that no new safety findings versus the previously submitted data were detected, the MAH proposed to include these additional safety data in the PI (section 4.8 "Pandemic Observational Study")
2. FUM 38: Outcome of Part B of the CSR of the MAH prepandemic study 810705 ("An Open-Label Phase 3 Study to Assess the Safety and Immunogenicity of a Vero Cell-Derived Whole Virus H5N1 Influenza Vaccine in an Adult and Elderly Population as well as in Specified Risk Groups") lead to update of section 4.8 of H1N1 SPC (H5N1). This report was submitted for Vepacel (an H5N1 pre-pandemic vaccine using the same vaccine construct) application for marketing authorization (EMEA/H/C/002089) on 20 Oct 2010 (no AR yet available). The respective H5N1 safety table in the H1N1 SmPC has been updated to reflect the outcome of Part B of the CSR of the prepandemic study 810705 (safety results in immunocompromised and chronically ill). Parts A and C of study 810705 were previously submitted on 30 Nov 2009 and 30 Dec 2009, and the safety outcome of FUM 38 was included in section 4.8 of the H1N1 SmPC with Variation EMEA/H/C/982/II/09.
3. FUM 39: Results from the Part B Day 181 CSR of the adult study 820902 ("An Open Label Phase I/II Study to Assess Immunogenicity and Safety of Different Dose Levels of H1N1 Pandemic Influenza Vaccine in Healthy Adults Aged 18 Years and Older") lead to the update of section 5.1 (H1N1). The report was previously submitted on 30 Jul 2010 and the AR of 27 September 2010 and outcome fax of 27 October 2010 are annexed to this report. Thus, data on persistence of anti-

HA antibodies 180 days after the first vaccination as measured by single radial haemolysis (SRH) and microneutralisation assay (MN) in adults aged 18 to 59 years and in elderly subjects aged 60 years and above, are now proposed to be included in section 5.1.

4. FUM 40: Results in infants and children aged 6 to 35 months (SRH & MN) in accordance with the results of Part A Day 43 report of the paediatric study 820903 ("An Open-Label Phase I/II Study to Assess the Immunogenicity and Safety of 2 Different Dose Levels of H1N1 Pandemic Influenza Vaccine in Healthy Infants, Children and Adolescents Aged 6 Months to 17 Years") lead to the update of section 5.1 and section 4.8 (H1N1). The report was previously submitted on 30 July 2010 and the AR of 11 October 2010 and outcome fax of 27 October 2010 are annexed to this report.

   The respective immunogenicity tables in section 5.1 of the SmPC ("Infants and children aged 6-35 months") have now been updated for SRH and MN results.

5. PSU 43: The inclusion of hypoaesthesia and abdominal pain as post-marketing adverse reactions (ADR) in 4.8 of the SmPC, as proposed by the MAH in the first full PSUR covering the 06 Oct 2009 to 30 Apr 2010, was requested in the 7 Dec 2010 outcome fax and AR for that PSUR of 26 Oct 10 (see annexed).

Analysis of data submitted

The purpose of this variation was the revision of the product information of Celvapan to reflect the outcome of the assessment of data available from the following post authorisation commitments:

SOB 30

The interim report was based on 2796 subjects (9 months and older) enrolled in the observational safety study. Following assessment of the safety data provided it was concluded that no new safety findings have been detected. Therefore these preliminary results from the pandemic observational study with Celvapan (H1N1)v confirmed the safety profile as observed in the clinical studies.

FUM 38 (H5N1)

In study 810705 subjects were enrolled into three cohorts to receive different formulations of a H5N1 whole virion, Vero cell derived candidate vaccine.

- Cohort 1: approximately 2960 healthy male and female subjects in two strata:
  1. Stratum A: approximately 2780 subjects aged 18 to 59 years
  2. Stratum B: approximately 180 subjects aged 60 years and older
- Cohort 2: approximately 300 immune compromised subjects aged 18 years and older
- Cohort 3: approximately 300 chronically ill patients aged 18 years and older

Safety was assessed in terms of adverse events (AEs) after vaccination. The primary safety endpoint was the occurrence of systemic reactions within 21 days after vaccination. Secondary safety endpoints have comprised frequency and severity of injection site reactions following vaccination; fever, malaise or shivering within 7 days of vaccination; and frequency and severity of AEs during the entire study period. Fever was rated according to the FDA Toxicity Grading Scales for vaccine trials.

Subjects in Cohort 1 were enrolled into four treatment groups. During study Part A, subjects in both age strata of Treatment group 1 and 2 received two vaccinations at the same dose level of either 7.5µg and 3.75 µg of the A/Vietnam/1203/2004 strain, respectively. Subjects in Treatment groups 3 and 4

included adult subjects aged 18 to 59 years only, all of whom received two vaccinations with the 7.5 µg dose level. During study Part B, subjects in Cohorts 2 and 3 received two vaccinations with a 7.5 µg dose level of the A/Vietnam/1203/2004 strain.

During study Part A, 2790 healthy subjects aged 18 to 59 years and 180 subjects aged ≥ 60 years received a first vaccination with the inactivated, whole virus, Vero cell-derived H5N1 vaccine administered by intramuscular injection and were included in the safety analysis dataset for the first vaccination. A total of 2741 adult subjects and 178 elderly subjects received a second vaccination at the same dose as they received for the first vaccination. During Part B, 319 immunocompromised subjects aged 18 years and older received the first vaccination and 311 subjects also received the second vaccination. A total of 300 chronically ill subjects aged 18 years and older received a first vaccination and 284 subjects also received the second vaccination.

Analysis of the safety data demonstrated that a two-dose vaccination regimen of H5N1 vaccine given 21 days apart was generally well tolerated. The primary endpoint was the frequency and severity of systemic reactions until 21 days after the first and second vaccination. The majority of subjects experienced no systemic reactions within 21 days after the first vaccination and the systemic reactions after both vaccinations were mostly mild to moderate and resolved within 24 hours.

After the first vaccination, systemic reactions were reported by 685/2730 (25.1%) subjects in the 7.5 µg dose group and by 20/60 (33.3%) in the 3.75 µg dose group in Stratum A. In Stratum B, subjects with systemic reactions numbered 26/120 (21.7%) in the 7.5 µg dose group and 13/60 (21.7%) in the 3.75 µg dose group.

After the second vaccination, systemic reactions were reported by 347/2684 (12.9%) subjects in the 7.5 µg dose group and by 9/57 (15.8%) in the 3.75 µg dose group in Stratum A. In Stratum B, 16/119 (13.4%) subjects in the 7.5 µg dose group and 7/59 (11.9%) in the 3.75 µg dose group experienced systemic reactions.

As regards the overall adverse reaction rates the majority of subjects experienced no injection site reactions within 21 days after the first vaccination and the injection site reactions after both vaccinations were mostly mild in severity.

After the first vaccination, injection site reactions were reported by 352/2730 (12.9%) subjects in the 7.5 µg dose group and by 10/60 (16.7%) in the 3.75 µg dose group in Stratum A. In Stratum B, subjects with injection site reactions numbered 12/120 (10.0%) in the 7.5 µg and 3/60 (5.0%) in the 3.75 µg dose group.

After the second vaccination, injection site reactions were reported by 295/2684 (11.0%) subjects in the 7.5 µg dose group and by 7/57 (12.3%) in the 3.75 µg dose group in Stratum A. In Stratum B, 8/119 (6.7%) subjects in the 7.5 µg dose group and 4/59 (6.8%) in the 3.75 µg dose group experienced injection site reactions.

Fever rates with onset within 7 days after vaccination were low. The highest point estimate was 1.6% after the first vaccination in Stratum A of the 7.5µg group; no fever occurred after the first or second vaccination in either age stratum of the 3.75 µg dose group. The highest rates of malaise (11.7%) and shivering (13.3%) occurred after the first vaccination in Stratum A of the 3.75 µg dose group. All three symptoms were mainly mild and moderate in severity. The most frequently-reported specifically queried symptoms of systemic reactions commonly associated with vaccination were headache (15.0%) and fatigue (11.7%) in the 3.75 µg dose group of Stratum A. The most common injection site reaction was injection site pain in Stratum A (11.0% and 11.7% in the 3.75 µg and 7.5 µg dose group), and ecchymosis in Stratum B (6.7% in 7.5 µg dose group).

Rates of injection site reactions after the first vaccination were low: 12.9% and 16.7% in Stratum A, and 10.0% and 5.0% in Stratum B, in the 7.5µg and 3.75µg dose groups respectively. Local reaction rates were generally lower after the second vaccination.

Nineteen subjects experienced a treatment-emergent SAE during study Part A (9 after the first and 10 after the second vaccination). Of these, five (three after the first, and two after the second vaccination) had an SAE considered related to the study vaccine: one subject experienced severe asthenia, pyrexia, and headache; one subject developed severe vestibular neuronitis; other subjects reported moderate influenza-like illness, rheumatoid arthritis and severe tension headache. There were no deaths.

A total of 319 immunocompromised subjects received the first vaccination and 311 also received the second. Systemic reaction rates were 28.5% after the first vaccination and 16.7% after the second; fever rate within 7 days after the first vaccination was 1.9%. Local reactions occurred at rates of 12.5% and 8.4% after the first and second vaccination, respectively. The most frequently reported symptoms of local and systemic reactions were injection site pain (10.0%), fatigue (9.1%), headache (8.8%) and muscle pain (7.2%) after the first vaccination. Adverse reactions were predominantly mild in severity and the majority resolved within 24 hours. There were no deaths and no serious adverse reactions.

A total of 300 chronically ill subjects aged 18 years and older received the first vaccination with the H5N1 vaccine and 284 subjects also received the second. Systemic reaction rates were 36.7% after the first vaccination and 20.1% after the second; the fever rate within 7 days after the first vaccination was 2.7%. Local reactions occurred at rates of 17.0% and 13.4% after the first and second vaccination, respectively. The most frequently reported symptoms of local and systemic reactions after the first vaccination were injection site pain (11.3%), fatigue (13.3%) and headache (10.7%). There were no deaths and no serious adverse reactions.

FUM 39

The final clinical study report on the safety and immunogenicity evaluation from Day 43 to Day 181 of adults and elderly subjects enrolled in clinical trial 820902 was previously submitted and assessed. The immunogenicity evaluation of antibody persistence up to 180 days of adult and elderly subjects who received at least one dose of Celvapan H1N1 revealed a moderate decline of the antibody response rates. The decline in seroprotective / seroneutralising response rates and GMTs up to 181 was consistent in both age strata and the response rates were comparable to those observed at Day 21 post dose 1.

FUM 40

The MAH provided the final Day43 CSR for study 820903 performed in children and adolescents, which was previously assessed. Due to problems with enrolment of very young children only 33 infants has been included finally in the ITT population and received at least one vaccine dose. Based on the MN assay 100% of the children, who received the 7.5µg vaccine dose, elicited MN-titers of at least 1:40 post dose 2. In this group a GMT of 303 was achieved. Response rates and antibody titres as measured by the HI and SRH assay were found to be generally lower.

As regards the capability of the vaccine to boost the antibody response, a significant increase in neutralising antibody titers was observed post dose 2 (GMR of 60.6). The booster effect was however less pronounced if the HI or SRH assay was used.

PSU 43

Following assessment of the first full PSUR the proposal of the MAH to include hypoaesthesia and abdominal pain as adverse reactions in section 4.8 of the SmPC was endorsed.

Discussion

The occurrence and frequency of adverse events following vaccination of healthy subjects with whole virion inactivated influenza H5N1 vaccine was comparable to the safety profile reported for the H1N1 vaccine formulation of Celvapan.

The safety profile of the H5N1 vaccine formulation was generally well tolerated in immunocompromised and chronically ill subjects and it was comparable with the safety profile observed in healthy subjects.

These data were regarded as supportive safety information for Celvapan H1N1 however the information in section 4.8 should be focused on the experience with H1N1 thus the MAH was asked to shorten the paragraph.

The data on persistence of anti-HA antibodies 180 days after the first vaccination as measured by single radial haemolysis (SRH) and microneutralisation assay (MN) in adults aged 18 to 59 years and in elderly subjects aged 60 years and above was reflected in section 5.1 of the SmPC.

The above immunogenicity data in children was used to amend the results tables in section 5.1 related to Infants and children aged 6–35 months.

Of note the information in section 5.1 on non-clinical studies with H5N1 vaccine was deemed no longer meaningful for health care providers and thus was replaced by a brief description on vaccine effectiveness gained with H1N1 in children in season 2009/2010 in Jersey, to inform that there were no reported vaccine failures in either of the paediatric age groups analysed. Crude vaccine effectiveness of one dose of pandemic vaccine among children was 100% (95% CI: 70-100%).

Changes to the Product Information

Sections 4.8 and 5.1 of the SmPC were revised in order to reflect data on antibody persistence (FUM 39, section 5.1), the latest immunogenicity data reported for infants and children (FUM 40, section 5.1) and safety information (SOB 30, FUM 38 and PSU 43, section 4.8).

With regard to SOB 30, the proposal to include the information in section 4.8 that preliminary results from the pandemic observational study with Celvapan (H1N1)v confirmed the safety profile as observed in the clinical studies was endorsed by the CHMP.

Following the first review the PI was further amended as follows:

- To shorten the paragraph on safety information reported for H5N1 in section 4.8.
- To replace the non-clinical information in section 5.1 with a brief summary on vaccine effectiveness in children.

To update Annex II conditions and to delete the DDPS version number following CHMP procedural announcement in October 2010.

Furthermore a couple of editorial mistakes were corrected in section 4.2.

In section 4.6 the information on animal studies were amended to correctly link them to the strain used.

The product information and the package leaflet were updated by the MAH and the changes were accepted by the CHMP.

The amended product information is given as attachment (see annexes) to this assessment report.

Conclusions and Benefit/Risk Assessment

The MAH filed a group of 5 variations as requested to include new information in sections 4.8 and 5.1 of the SmPC and in section 4 of the PL. In summary:

Section 4.8 was revised based on new data obtained from post-marketing experience; hypoaesthesia and abdominal pain were include as adverse reactions. Section 5.1 was updated to reflect that antibody persistence up to 180 days in adult and elderly subjects who received at least one dose of Celvapan H1N1 revealed a moderate decline of the antibody response rates. The latest immunogenicity data reported for infants and children aged 6–35 months was included in section 5.1. The information in section 5.1 on non-clinical studies with H5N1 vaccine was replaced by a brief description on vaccine effectiveness gained with H1N1 in children in the season 2009/2010 in Jersey, to inform that there were no reported vaccine failures in either of the paediatric age groups analysed and that crude vaccine effectiveness of one dose of pandemic vaccine among children was 100%.

The proposed revision of the product information was endorsed by the CHMP.

The currently available immunogenicity and safety data from clinical trials and post-marketing experience have no negative impact on the benefit-risk balance of Celvapan.

2. Conclusion

On 14 April 2011 the CHMP considered the following variations to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet

Variation(s) requested		**Type**
C.I.4	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II
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Group of 5 type II variations (C.I.4) to update of sections 4.8 and 5.1 of the SmPC further to the evaluation of clinical follow-up measures (FUMs 30, 38, 39 & 40) and of the PSUR covering the period

from 6 October 2009 to 30 September 2010 as requested by the CHMP. The section 4 of the PL has been updated accordingly. The MAH took the opportunity to correct mistakes in section 4.2 and 4.6 of the SmPC, to update the contact details for the local representatives in the PL in line with the latest QRD template, to delete the DDPS version number as per CHMP October 2010 request, and to update Annex II other conditions as requested by the CHMP.

3. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

EPAR scope

Group of 5 type II variations (C.I.4) to update of sections 4.8 and 5.1 of the SmPC further to the evaluation of clinical follow-up measures (FUMs 30, 38, 39 & 40) and of the PSUR covering the period from 6 October 2009 to 30 September 2010 as requested by the CHMP. The section 4 of the PL has been updated accordingly. The MAH took the opportunity to correct mistakes in section 4.2 and 4.6 of the SmPC, to update the contact details for the local representatives in the PL in line with the latest QRD template, to delete the DDPS version number as per CHMP October 2010 request, and to update Annex II other conditions as requested by the CHMP.

Summary

Section 4.8 was revised based on new data obtained from post-marketing experience; hypoaesthesia and abdominal pain were include as adverse reactions. Section 5.1 was updated to reflect that antibody persistence up to 180 days in adult and elderly subjects who received at least one dose of Celvapan H1N1 revealed a moderate decline of the antibody response rates. The latest immunogenicity data reported for infants and children aged 6–35 months was included in section 5.1. The information in section 5.1 on non-clinical studies with H5N1 vaccine was replaced by a brief description on vaccine effectiveness gained with H1N1 in children in the season 2009/2010 in Jersey, to inform that there were no reported vaccine failures in either of the paediatric age groups analysed and that crude vaccine effectiveness of one dose of pandemic vaccine among children was 100%.