



European Medicines Agency

London, 17 December 2009
EMA/843807/2009

**ASSESSMENT REPORT
FOR
Celvapan**

International Nonproprietary Name:
pandemic influenza vaccine (H1N1) (whole virion, virus cell derived, inactivated)
A/California/07/2009 (H1N1)v

Procedure No. EMEA/M/C/982/II/0009

Marketing Authorisation Holder/Applicant: 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

Celvapan is a pandemic H1N1v vaccine. The strain change of the mock-up vaccine from H5N1 to H1N1v was approved on 06/10/2009 (EMEA/H/C/982/PU/02). As committed by the marketing authorisation holder (MAH), preliminary safety data from the ongoing clinical trial in adults and elderly evaluating different H1N1v vaccine formulations was submitted. Additional data from the ongoing trial in adults and elderly evaluating different H5N1 vaccine formulation was submitted. Post-marketing experience was reflected in the first sPSUR. Following assessment of this data, the MAH was requested to update the product information to reflect the current safety information available. The variation was submitted on 2 December 2009.

2. CLINICAL

Assessment

Study 820902 adults (including the elderly)

Design and demographics of clinical study 820902

Study **820902** is a phase I/II prospective, randomised, open label, multicentre study designed to assess immunogenicity and safety of an investigational H1N1 pandemic influenza vaccine in healthy subjects aged 18 years of age and older.

Primary Objective

The primary objective of the study is to measure the immune response, as determined by HI (haemagglutination inhibition) assay.

Secondary Objectives

- To assess the immune response as determined by microneutralisation (MN) assay
- To identify the optimal dose level of an investigational H1N1 pandemic influenza vaccine
- To investigate the safety characteristics

Subjects were recruited in equal numbers to two age strata of 18 to 59 years of age (Stratum A) and 60 years of age and older (Stratum B). Within each stratum, subjects were randomised 1:1 to receive two intramuscular injections of the whole virion, Vero cell-derived influenza vaccine at the same dose level of either 3.75 µg or 7.5 µg of H1N1v (A/California/07/2009) HA antigen (Cohort 1) on Day 1 and Day 22. Cohort 1 consists of approximately 400 subjects (200 adults, 200 elderly).

| Dose Level | Cohort | Adults 18-59 Years | Elderly ≥ 60 Years |
|------------|--------|-----------------------|-----------------------|
| 7.5 µg | 1 | 100 | 100 |
| 3.75 µg | 1 | 100 | 100 |

Enrollment started in August 2009 and 411 adult and elderly subjects were included in cohort 1. Subjects of cohort 1 were vaccinated twice with 7.5 µg or 3.75 µg HA of the pandemic vaccine 21 days apart. Currently safety data base (n= 408) of 21 days after each vaccination is available.

Summary of Preliminary Day 22 Safety results

The safety data provided differentiate between the two administered dose groups 3.75 µg and 7.5 µg, and distinguish between the two age groups of adults and elderly subjects.

The preliminary analysis of the safety data base throughout a 21 days observation period after the first vaccination demonstrates a favourable safety profile in regards to solicited local and systemic reactions (Table 1).

Table 1: Summary of adverse experiences reported after the first vaccination in adults and elderly

| Dose [µg] | Adults | | Elderly | |
|---------------------------|-----------------------|----------------------|-----------------------|-----------------------|
| | 3.5 N=103 n (%) | 7.5 N=99 n (%) | 3.5 N=100 n (%) | 7.5 N=101 n (%) |
| Injection site swelling | 0 | 1 (1.0) | 0 | 2 (2.0) |
| Injection site induration | 0 | 2 (2.0) | 0 | 1 (1.0) |
| Injection site redness | 0 | 1 (1.0) | 1 (1.0) | 1 (1.0) |
| Injection site pain | 6 (5.8) | 7 (7.1) | 4 (4.0) | 6 (5.9) |
| Injection site tenderness | 0 | 0 | 0 | 0 |
| Fatigue | 7 (6.7) | 7 (6.9) | 3 (2.9) | 7 (6.9) |
| Headache | 4 (3.8) | 9 (8.9) | 1 (1.0) | 2 (2.0) |
| Joint pain | 1 (1.0) | 1 (1.0) | 1 (1.0) | 2 (2.0) |
| Malaise | 3 (2.9) | 2 (2.0) | 1 (1.0) | 1 (1.0) |
| Muscle pain | 3 (2.9) | 4 (4.0) | 1 (1.0) | 3 (3.0) |
| Shivering | 0 | 0 | 0 | 0 |
| Sweating | 3 (2.9) | 4 (4.0) | 4 (3.9) | 5 (5) |

Table 2: Summary of adverse experiences reported after the second vaccination in adults and elderly

| Dose [µg] | Adults | | Elderly | |
|---------------------------|-----------------------|----------------------|-----------------------|-----------------------|
| | 3.5 N=103 n (%) | 7.5 N=99 n (%) | 3.5 N=100 n (%) | 7.5 N=101 n (%) |
| Injection site swelling | 0 | 1 (1.0) | 0 | 2 (2.0) |
| Injection site induration | 0 | 2 (2.0) | 0 | 1 (1.0) |
| Injection site redness | 0 | 1 (1.0) | 1 (1.0) | 1 (1.0) |
| Injection site pain | 6 (5.8) | 7 (7.1) | 4 (4.0) | 6 (5.9) |
| Injection site tenderness | 0 | 0 | 0 | 0 |
| Fatigue | 7 (6.8) | 4 (4.0) | 6 (6.0) | 4 (4.0) |
| Headache | 7 (6.8) | 4 (4.0) | 3 (3.0) | 2 (2.0) |
| Joint pain | 1 (1.0) | 1 (1.0) | 2 (2.0) | 1 (1.0) |
| Malaise | 2 (1.9) | 1 (1.0) | 0 | 1 (1.0) |
| Muscle pain | 1 (1.0) | 0 | 1 (1.0) | 2 (2.0) |
| Shivering | 1 (1.0) | 1 (1.0) | 2 (2.0) | 0 |
| Sweating | 3 (2.9) | 0 | 2 (2.0) | 1 (1.0) |

Local reactions

Local reactions occurred at a low rate and mostly reported symptom was injection site pain in all dose groups as well as age groups ($\leq 5.8\%$ and $\leq 7.1\%$ in the 3.75 µg and 7.5 µg dose group). All other symptoms were reported at rates of $\leq 2.0\%$.

Table 14.3-8

Frequency and severity of injection site reactions occurring during the 7 days following the first vaccination (Study 820902 - Day 43 HI Report: Subjects included in the safety dataset)

| Stratum | Dose group | Statistics | None | Mild | Moderate | Unknown | Severe | Total |
|----------------|------------|------------|----------------|--------------|-------------|--------------|-------------|--------------|
| A(18-59 years) | 3.75ug | n/N (%) | 100/104(96.2%) | 4/104 (3.8%) | 0/104(0.0%) | 0/104 (0.0%) | 0/104(0.0%) | 4/104 (3.8%) |
| A(18-59 years) | 7.5ug | n/N (%) | 92/101(91.1%) | 9/101 (8.9%) | 0/101(0.0%) | 0/101 (0.0%) | 0/101(0.0%) | 9/101 (8.9%) |
| B(60+ years) | 3.75ug | n/N (%) | 97/102(95.1%) | 5/102 (4.9%) | 0/102(0.0%) | 0/102 (0.0%) | 0/102(0.0%) | 5/102 (4.9%) |
| B(60+ years) | 7.5ug | n/N (%) | 98/101(97.0%) | 3/101 (3.0%) | 0/101(0.0%) | 0/101 (0.0%) | 0/101(0.0%) | 3/101 (3.0%) |

Table 14.3-9
Frequency and severity of injection site reactions occurring during the 7 days following the second vaccination
(Study 820902 - Day 43 HI Report: Subjects included in the safety dataset)

| Stratum | Dose group | Statistics | None | Mild | Moderate | Unknown | Severe | Total |
|----------------|------------|------------|---------------|--------------|-------------|--------------|-------------|--------------|
| A(18-59 years) | 3.75ug | n/N (%) | 97/103(94.2%) | 6/103 (5.8%) | 0/103(0.0%) | 0/103 (0.0%) | 0/103(0.0%) | 6/103 (5.8%) |
| A(18-59 years) | 7.5ug | n/N (%) | 91/99(91.9%) | 7/99 (7.1%) | 0/99(0.0%) | 1/99 (1.0%) | 0/99(0.0%) | 8/99 (8.1%) |
| B(60+ years) | 3.75ug | n/N (%) | 95/100(95.0%) | 5/100 (5.0%) | 0/100(0.0%) | 0/100 (0.0%) | 0/100(0.0%) | 5/100 (5.0%) |
| B(60+ years) | 7.5ug | n/N (%) | 95/101(94.1%) | 6/101 (5.9%) | 0/101(0.0%) | 0/101 (0.0%) | 0/101(0.0%) | 6/101 (5.9%) |

Local reactions were considered by subjects always mild and only for one case it was recorded as unknown severity.

Systemic Reactions within 21 Days after the First and Second Vaccination

The majority of subjects experienced no systemic reactions within 7 days after either vaccination. After the first vaccination, rates of subjects who reported systemic reactions were 18.8% and 12.5% in the 7.5 µg and 3.75 µg dose group in Stratum A and 16.8% and 11.8% in the 7.5 µg and 3.75 µg dose group in Stratum B (Table 1).

Rates of subjects who reported systemic reactions within 7 days after the second vaccination were generally slightly lower: 13.1% and 13.6% in the 7.5 µg and 3.75 µg dose group in Stratum A and 8.9% and 10.0% in the 7.5 µg and 3.75 µg dose group in Stratum B (Table 2).

Table 14.3-10
Frequency and severity of systemic reactions occurring during the 7 days following the first vaccination
(Study 820902 - Day 43 HI Report: Subjects included in the safety dataset)

| Stratum | Dose group | Statistics | None | Mild | Moderate | Unknown | Severe | Total |
|----------------|------------|------------|---------------|----------------|-------------|--------------|-------------|----------------|
| A(18-59 years) | 3.75ug | n/N (%) | 91/104(87.5%) | 13/104 (12.5%) | 0/104(0.0%) | 0/104 (0.0%) | 0/104(0.0%) | 13/104 (12.5%) |
| A(18-59 years) | 7.5ug | n/N (%) | 82/101(81.2%) | 19/101 (18.8%) | 0/101(0.0%) | 0/101 (0.0%) | 0/101(0.0%) | 19/101 (18.8%) |
| B(60+ years) | 3.75ug | n/N (%) | 90/102(88.2%) | 11/102 (10.8%) | 1/102(1.0%) | 0/102 (0.0%) | 0/102(0.0%) | 12/102 (11.8%) |
| B(60+ years) | 7.5ug | n/N (%) | 84/101(83.2%) | 16/101 (15.8%) | 1/101(1.0%) | 0/101 (0.0%) | 0/101(0.0%) | 17/101 (16.8%) |

Table 14.3-11
Frequency and severity of systemic reactions occurring during the 7 days following the second vaccination
(Study 820902 - Day 43 HI Report: Subjects included in the safety dataset)

| Stratum | Dose group | Statistics | None | Mild | Moderate | Unknown | Severe | Total |
|----------------|------------|------------|---------------|----------------|-------------|--------------|-------------|----------------|
| A(18-59 years) | 3.75ug | n/N (%) | 89/103(86.4%) | 12/103 (11.7%) | 2/103(1.9%) | 0/103 (0.0%) | 0/103(0.0%) | 14/103 (13.6%) |
| A(18-59 years) | 7.5ug | n/N (%) | 86/99(86.9%) | 13/99 (13.1%) | 0/99(0.0%) | 0/99 (0.0%) | 0/99(0.0%) | 13/99 (13.1%) |
| B(60+ years) | 3.75ug | n/N (%) | 90/100(90.0%) | 9/100 (9.0%) | 1/100(1.0%) | 0/100 (0.0%) | 0/100(0.0%) | 10/100 (10.0%) |
| B(60+ years) | 7.5ug | n/N (%) | 92/101(91.1%) | 8/101 (7.9%) | 1/101(1.0%) | 0/101 (0.0%) | 0/101(0.0%) | 9/101 (8.9%) |

Overall, the majority of systemic reactions were mild and none were severe (Table 14.3-10 and Table 14.3-11).

Certain symptoms of systemic reactions (fatigue, headache, sweating, muscle pain, joint pain, shivering and fever) with onset later than Day 6 after vaccination) were specifically queried in the subject diary. Fatigue and headache were the most frequently reported symptoms overall. After the first vaccination, there was a slightly higher risk of experiencing fatigue, headache, joint pain, muscle pain or sweating, with the 7.5 µg dose observed relative to the 3.75 µg dose in Stratum A, and for all symptoms except shivering in Stratum B.

Fever

No fever with onset within 7 days after either vaccination was reported in Stratum A; in Stratum B, one incidence of mild fever occurred within 7 days after the first vaccination among subjects who received a 3.75 µg vaccine dose.

SAEs

Two serious adverse events (SAEs) considered unrelated occurred within 21 days after vaccination:

- pulmonary embolism (10 days after vaccination) and
- one case of dialysis of the retina of the right eye; the patient was hospitalised for surgery.

Some events, which might be summarised as allergic reactions were observed, such as burning eyes, warm sensation at vaccination site, exanthema and allergic rhinitis.

The stratification into the age groups of adults and elderly subjects revealed no difference in the frequency and severity of adverse events post dose 1 except for headache, which occurred more often in adults (~12%) than in elderly subjects (5%).

Study 810705 (> 18 years)

Study Design:

This is a Phase III open-label clinical study in male and female subjects (3560 planned), stratified to three cohorts, two age strata and four treatment groups to assess the safety and immunogenicity of Baxter's Vero cell-derived whole virus H5N1 influenza vaccine in an adult and elderly population as well as in specified risk groups. For a subset of subjects in two cohorts, antibody kinetics and T-cell mediated immune response will also be evaluated.

Objectives:

The objectives of this study are:

- To assess the safety and tolerability of a non-adjuvanted H5N1 influenza vaccine in an adult and elderly population and in specified risk groups;
- To assess the immune response to a non-adjuvanted H5N1 influenza vaccine in an adult and elderly population and in specified risk groups;
- To assess persistence of H5N1 influenza antibodies after vaccination with a non-adjuvanted H5N1 influenza vaccine in an adult and elderly population

and in specified risk groups:

- To demonstrate consistency of immune response among three different lots of a non-adjuvanted H5N1 influenza vaccine.

For the subset of subjects included in the evaluation of cellular immunity a further objective of the study is:

- To evaluate the T-cell mediated immune response induced by an H5N1 influenza vaccine after the first and second vaccinations.

Number of subjects:

Planned: 3560 overall

Subjects were enrolled into three cohorts as follows:

- Cohort 1: approximately 2960 healthy male and female subjects in two strata:
 - Stratum A: approximately 2780 subjects aged 18 to 59 years
 - 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

Analyzed (Part A safety):

The safety analysis dataset for each vaccination included the following subjects:

1st vaccination:

- 2790 Stratum A (7.5 µg N = 2730, 3.75 µg N = 60)
- 180 Stratum B (7.5 µg N = 120, 3.75 µg N = 60)

2nd vaccination:

- 2743 Stratum A (7.5 µg N = 2684, 3.75 µg N = 57)
- 119 Stratum B (7.5 µg N = 119, 3.75 µg N = 59)

Safety is assessed in all subjects in terms of AEs occurring after vaccination. A subject diary is distributed after each vaccination in which subjects are to record any injection site reactions, systemic AEs, other AEs, daily oral body temperature (digital thermometer provided) until Day 6 after vaccination, medication taken after vaccination, and information on travel to countries or regions in which human H5N1 influenza infections have been reported in the past. The 3-person independent Data Monitoring Committee (DMC) reviews and evaluates all SAE reports. For subjects participating in the evaluation of cellular immunity, a haematology and differential blood count analysis is performed on Day 0, Day 21, Day 42 and Day 201. ALT and Ca values are determined after the first and second vaccination for approximately 100 subjects in Cohort 2 participating at German study sites and approximately 100 subjects in Cohort 3. Calcium concentration is also determined in all subjects in Cohort 1, Treatment groups 1 and 2.

Brief Summary of Adverse Events

SAEs

Nineteen (19) subjects experienced a treatment-emergent SAE during study Part A (nine after the first and ten 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:

- severe asthenia, pyrexia, and headache;
- severe vestibular neuronitis;
- moderate influenza-like illness;
- rheumatoid arthritis and
- severe tension headache.

There were no deaths.

Overview of Adverse Reactions Occurring During Part A

The overall adverse reaction rates after the first vaccination were 31.9% in the 7.5 µg dose group and 38.3% in the 3.75 µg dose group in Stratum A, and 27.5% in the 7.5 µg dose group and 25.0% in the 3.75 µg dose group in Stratum B.

After the second vaccination, rates of subjects with any adverse reactions were somewhat lower: 20.2% in the 7.5 µg dose group and 19.3% in the 3.75 µg dose group in Stratum A, and 17.6% in the 7.5 µg dose group and 16.9% in the 3.75 µg dose group in Stratum B.

The primary endpoint was the frequency and severity of systemic reactions until 21 days after the first and second vaccination. Systemic reaction rates in the 7.5 µg and 3.75 µg dose groups, respectively, after the first vaccination were 25.1% and 33.3% in Stratum A, and 21.7% and 21.7% in Stratum B; and after the second vaccination were 12.9% and 15.8% in Stratum A, and 13.4% and 11.9% in Stratum B. Systemic reactions occurring after both vaccinations were mostly mild and moderate.

Fever, Malaise and Shivering with onset within 7 days after the first and second vaccination

Table 14.3-10.
Number of subjects experiencing fever, malaise and shivering after the 1st and 2nd vaccination
(Study 810705: Subjects included in the safety dataset)

| Stratum | Dose group | Vaccination | Fever | | Malaise | | Shivering | |
|---------|------------|--------------------|----------------|------------|-----------------|-------------|-----------------|-------------|
| | | | n/N (%) | 95% C.I. | n/N (%) | 95% C.I. | n/N (%) | 95% C.I. |
| A | 7.5µg | first vaccination | 43/2711 (1.6%) | 1.2%; 2.1% | 196/2730 (7.2%) | 6.2%; 8.2% | 152/2730 (5.6%) | 4.7%; 6.5% |
| | | second vaccination | 17/2669 (0.6%) | 0.4%; 1.0% | 104/2684 (3.9%) | 3.2%; 4.7% | 68/2684 (2.5%) | 2.0%; 3.2% |
| | 3.75µg | first vaccination | 0/60 (0.0%) | 0.0%; 6.0% | 7/60 (11.7%) | 4.8%; 22.6% | 8/60 (13.3%) | 5.9%; 24.6% |
| | | second vaccination | 0/57 (0.0%) | 0.0%; 6.3% | 1/57 (1.8%) | 0.0%; 9.4% | 1/57 (1.8%) | 0.0%; 9.4% |
| B | 7.5µg | first vaccination | 1/119 (0.8%) | 0.0%; 4.6% | 5/120 (4.2%) | 1.4%; 9.5% | 6/120 (5.0%) | 1.9%; 10.6% |
| | | second vaccination | 1/119 (0.8%) | 0.0%; 4.6% | 5/119 (4.2%) | 1.4%; 9.5% | 5/119 (4.2%) | 1.4%; 9.5% |
| | 3.75µg | first vaccination | 0/60 (0.0%) | 0.0%; 6.0% | 1/60 (1.7%) | 0.0%; 8.9% | 2/60 (3.3%) | 0.4%; 11.3% |
| | | second vaccination | 0/59 (0.0%) | 0.0%; 6.1% | 2/59 (3.4%) | 0.4%; 11.7% | 5/59 (8.5%) | 2.8%; 18.7% |

There was no **fever** with onset within 7 days after either the first or second vaccination, among subjects who received 3.75 µg HA antigen and fever rates were low with the 7.5 µg dose. After the first vaccination with a 7.5 µg dose, 43/2711 (1.6%; 95% CI 1.2%; 2.1%) of subjects in Stratum A and 1/119 (0.8%; 95% CI 0.0%; 4.6%) in Stratum B reported fever.

Following the second vaccination with 7.5 µg HA antigen, subjects who experienced fever after the second vaccination numbered 17/2669 (0.6%; 95% CI 0.4%; 1.0%) in Stratum A and 1/119 (0.8%; 95% CI 0.0%; 4.6%) in Stratum B (Table 14.3-10).

Malaise with onset within 7 days after the first vaccination was reported by 196/2730 (7.2%; 95% CI 6.2% ; 8.2%) subjects in the 7.5 µg dose group and by 7/60 (11.7%; 95% CI 4.8% ; 22.6%) in the 3.75 µg dose group in Stratum A. Subjects in Stratum B who experienced malaise after the first vaccination numbered 5/120 (4.2%; 95% CI 1.4% ; 9.5%) in the 7.5 µg dose group and 1/60 (1.7%; 95% CI 0.0% ; 8.9%) in the 3.75 µg dose group. Following the second vaccination, 104/2684 (3.9%; 95% CI 3.2%; 4.7%) subjects in the 7.5 µg dose group and 1/57 (1.8%; 95% CI 0.0%; 9.4%) in the 3.75 µg dose group in Stratum A reported malaise. Subjects in Stratum B who experienced malaise after the second vaccination numbered 5/119 (4.2%; 95% CI 1.4%; 9.5%) in the 7.5 µg dose group and 2/59 (3.4%; 95% CI 0.4%; 11.7%) in the 3.75 µg dose group (Table 14.3-10).

Shivering with onset within 7 days after the first vaccination was experienced by 152/2730 (5.6%; 95% CI 4.7% ; 6.5%) subjects in the 7.5 µg dose group and by 8/60 (13.3%; 95% CI 5.9% ; 24.6%) in the 3.75 µg dose group in Stratum A. Subjects in Stratum B who reported shivering after the first vaccination numbered 6/120 (5.0%; 95% CI 1.9% ; 10.6%) in the 7.5 µg dose group and 2/60 (3.3%; 95% CI 0.4% ; 11.3%) in the 3.75 µg dose group. Following the second vaccination, 68/2684 (2.5%; 95% CI 2.0%; 3.2%) subjects in the 7.5 µg dose group and 1/57 (1.8%; 95% CI 0.0%; 9.4%) in the 3.75 µg dose group in Stratum A reported shivering. Subjects in Stratum B who experienced shivering after the second vaccination numbered 5/119 (4.2%; 95% CI 1.4%; 9.5%) in the 7.5 µg dose group and 5/59 (8.5%; 95% CI 2.8%; 18.7%) in the 3.75 µg dose group (Table 14.3-10).

All three symptoms (fever within 7 days after vaccination, malaise, shivering) were mainly mild to moderate in severity after each vaccination. Severe fever occurred in Stratum A subjects who received 7.5 µg HA antigen only (0.3% and 0.2% of subjects after the first and second vaccination). One of these subjects had a temperature of 40.3 for one day, which the investigator graded as severe based on the clinical assessment. According to the FDA toxicity grading scale fever >40°C may be considered potentially life-threatening.

Severe malaise and shivering also occurred among Stratum A subjects who received the 7.5 µg dose level only (malaise at a rate of 0.3% and 0.1% of subjects after the first and second vaccination, and shivering at rates of 0.2% and 0.1% after the first and second vaccination).

Rates of injection site reactions (mostly mild and moderate) 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.

Table 14.3-7.
Number of subjects experiencing any non serious injection site reactions after the 1st and 2nd vaccination
(Study 810705: Subjects included in the safety dataset)

| Stratum | Dose group | after 1st vaccination | | after 2nd vaccination | |
|-------------------------|------------|-----------------------|--------------|-----------------------|-------------|
| | | n/N (%) | 95% C.I. | n/N (%) | 95% C.I. |
| Stratum A (18-59 years) | 7.5µg | 352/2730 (12.9%) | 11.7%; 14.2% | 295/2684 (11.0%) | 9.8%; 12.2% |
| | 3.75µg | 10/60 (16.7%) | 8.3%; 28.5% | 7/57 (12.3%) | 5.1%; 23.7% |
| Stratum B (>= 60 years) | 7.5µg | 12/120 (10.0%) | 5.3%; 16.8% | 8/119 (6.7%) | 2.9%; 12.8% |
| | 3.75µg | 3/60 (5.0%) | 1.0%; 13.9% | 4/59 (6.8%) | 1.9%; 16.5% |

After the first vaccination, injection site reactions were reported by 352/2730 (12.9%; 95% CI 11.7%; 14.2%) subjects in the 7.5 µg dose group and by 10/60 (16.7%; 95% CI 8.3%; 28.5%) in the 3.75 µg dose group in Stratum A. In Stratum B, subjects with injection site reactions numbered 12/120 (10.0%; 95% CI 5.3%; 16.8%) in the 7.5 µg and 3/60 (5.0%; 95% CI 1.0%; 13.9%) in the 3.75 µg dose group (Table 14.3-7).

Table 14.3-9.
Number of subjects with non serious injection site reactions within 21 days after the 2nd vaccination by severity
(Study 810705: Subjects included in the safety dataset)

| Stratum / Dose group | | Severity of injection site reactions | | | | | | | | | | |
|-------------------------|--------|--------------------------------------|--------|-------------|---------|------|---------|----------|--------|--------|--------|-------|
| | | NAV | | No reaction | | Mild | | Moderate | | Severe | | Total |
| | | N | % | N | % | N | % | N | % | N | % | |
| Stratum A (18-59 years) | 7.5µg | 3 | (0.1%) | 2389 | (89.0%) | 255 | (9.5%) | 3 | (1.3%) | 3 | (0.1%) | 2684 |
| | 3.75µg | 0 | (0.0%) | 50 | (87.7%) | 6 | (10.5%) | 1 | (1.8%) | 0 | (0.0%) | 57 |
| Stratum B (>= 60 years) | 7.5µg | 0 | (0.0%) | 111 | (93.3%) | 7 | (5.9%) | 1 | (0.8%) | 0 | (0.0%) | 119 |
| | 3.75µg | 0 | (0.0%) | 55 | (93.2%) | 2 | (3.4%) | 2 | (3.4%) | 0 | (0.0%) | 59 |

After the second vaccination, injection site reactions were reported by 295/2684 (11.0%; 95% CI 9.8% ; 12.2%) subjects in the 7.5 µg dose group and by 7/57 (12.3%; 95% CI 5.1%; 23.7%) in the 3.75 µg dose group in Stratum A. In Stratum B, 8/119 (6.7%; 95% CI 2.9%; 12.8%) subjects in the 7.5 µg dose group and 4/59 (6.8%; 95% CI 1.9%; 16.5%) in the 3.75 µg dose group experienced injection site reactions (Table 14.3-7).

Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value

During study Part A, a slightly elevated Calcium level was determined in one subject on Day 21 only, where after normal values were recorded. One subject had a slightly higher value on Day 0 before vaccination, which returned to normal by Day 21. One subject had elevated Ca levels on Day 0 and Day 21, but a normal value on Day 42. Slightly elevated levels were recorded in three subjects at baseline and each subsequent visit during study Part A, and in four subjects on Day 42 only; follow-up information for these seven subjects is not yet available.

sPSUR 1

This first simplified Periodic Safety Update Report (S-PSUR) is a summary of data relevant for assessing the safety of Celvapan for the period from 14Oct2009 through 16Nov2009.

Vaccine distribution

Doses of Celvapan distributed to the EU member states from 14Oct2009 through 16Nov2009 were 3 399 200 (Austria 918 400 doses, France 12 000 doses, Germany 92 600, Ireland 230 800, UK 2145 400) and outside the EU 198 600.

Data on the actual exposure of Celvapan are currently not available to Baxter. The exposure is dependent on the utilization of Celvapan within the national vaccination campaigns. It can currently be estimated that of the Celvapan volumes distributed, as shown above, significant amounts have not yet been used. When more detailed information on actual exposure is made available by the national authorities, it will be included in subsequent S-PSUR/s.

Safety evaluation

During the period from 14Oct2009 up to and including 16Nov2009, a total of 146 reports of suspected adverse reactions to H1N1 vaccine have been received by Baxter from the spontaneous reporting system. These 146 reports include 566 suspected adverse reactions.

A breakdown of the number of adverse reaction reports received by vaccine brand is provided in the table below:

| Vaccine | Number of adverse reaction reports | | | | |
|---------------------------------|------------------------------------|--------|-------------|--------|-------|
| | Serious | | Non-serious | | Total |
| | Unlisted | Listed | Unlisted | Listed | |
| Celvapan | 46 | 7 | 26 | 9 | 88 |
| H1N1 vaccine, brand unspecified | 24 | 2 | 24 | 8 | 58 |
| Total | 70 | 9 | 50 | 17 | 146 |

Reported suspected adverse reactions

A total of 88 adverse reaction reports for Celvapan were received for this reporting period. The most frequently reported adverse reactions were nausea (n=16), fatigue (n=16), headache (n=15), pyrexia (n=14), dizziness (n=13), vomiting (n=12) and hypersensitivity (n=11). Except for hypersensitivity, all other before-mentioned terms are listed adverse reactions for Celvapan.

Fatal reactions

No reports

AESIs

Neuritis

1 case of possible neuritis (reported terms numbness in the ring and pinky fingers of the left hand and paraesthesia extending to the adjacent metacarpus). Events were not resolved at time of reporting. The case was assessed by Baxter as serious and unlikely associated given the very short latency of 2 minutes.

Anaphylactic reaction / Angioedema

A narrow SMQ query for anaphylactic reaction / angioedema revealed 12 reports for this SMQ. A review of all 12 narratives revealed 4 reports indicative for an anaphylactic reaction with level 1-3 of Brighton Collaboration cases definition diagnostic certainty (3 reports from Ireland, 1 from Austria) and 3 additional reports were evaluated regarding a possible angioedema.

All 4 cases were assessed as probably/possibly associated due to the reasonable temporal association between the Celvapan vaccination and the onset of events. No lot association was identified for the above-mentioned cases of anaphylactic reaction.

Based on the very limited information regarding a sudden onset of symptoms as defined for an angioedema as well as the clinical course of these events, a diagnosis of angioedema was not considered for any of the 3 cases.

3. OVERALL DISCUSSION AND BENEFIT-RISK ASSESSMENT

CHMP noted that preliminary data reported for the ongoing H1N1v and H5N1 studies in adults (including the elderly) suggest a comparable safety profile for both vaccine formulations. In parallel the first sSPUR was assessed within the variation, which caused an updated safety profile in the post-marketing surveillance in 4.8 of the SPC.

Adults (including the elderly) H1N1v

The data demonstrate a comparable safety profile to that observed for seasonal flu vaccines and in previous clinical trials with the H5N1 mock-up vaccine.

Safety analysis stratified into respective age strata for the adults and the elderly revealed that in general regardless of the vaccine formulation administered slightly more adverse reactions were reported for adults compared to elderly subjects. Only headache occurred more frequently in adults (~12%) than in the elderly (5.2%).

Day 21 safety data reported post-dose 2 did not differ from the post-dose 1 data.

Adults (including the elderly) H5N1

The majority of subjects who experienced symptoms reported symptoms of mild severity in all age groups regardless of the dose used. Very few symptoms of moderate severity were reported and local or systemic adverse reactions of severe severity were rarely reported. Following second vaccination the frequency of any adverse reactions were somewhat lower.

The safety data base was quite high in numbers of subject and therefore the following four new adverse reactions were included in the SPC, section 4.8. paresthesia, ear pain, dry throat and clumsiness of vaccinated arm, which were observed within the trial and were not mentioned before in the list of adverse reactions.

Although data on a very low number of subjects, especially in the lower age groups, is available, overall the safety database involving 146 subjects might suggest a favourable safety profile with regard to systemic reactions. This limited and preliminary information was included in the product information.

First sPSUR (children and adults)

During the period from 14 Oct 2009 up to and including 16 Nov 2009, a total of 146 reports of suspected adverse reactions to H1N1 vaccine have been received by Baxter from the spontaneous reporting system. These 146 reports include 566 suspected adverse reactions. The evaluation of the impact of these suspected adverse reactions caused changes in the SPC. Primarily four cases of anaphylactic reactions were reported, which were assessed as probably/possibly associated to the vaccine. Regarding angioedema, there were 2 serious cases that were evaluated with respect to a possible angioedema. However, in both cases the information was too limited to confirm the diagnosis. 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 is recommended to include these terms into the CCDS. The benefit-risk balance for Celvapan is considered to remain positive.

4. CHANGES TO THE PRODUCT INFORMATION

Further to the assessment and the scientific discussions held at the CHMP, the following changes to the Product Information were requested and subsequently implemented by the MAH:

Update on section 4.2 of the SPC to reflect that very limited safety data has been assessed during Variation II-006 as is reflected under 4.8.

The PL was updated accordingly.

5. CONCLUSION

Following the assessment of safety data of Study 820902 (part of SO 2 027.1), the Part A of Study 810705 (FUM C-038) and the sPSUR 1, it was requested that the new safety information should be included in the product information.

The MAH filed a variation as requested to include the information in section 4.2, 4.4 and 4.8 of the SPC and in section 2 and 4 of the PL.

The wording is endorsed by CHMP. The revised product information including also an update of section 4.2 to reflect that very limited safety data has been assessed during Variation II-06 is provided as an Annex.

On 17 December 2009 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.

Medicinal product no longer authorised