EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Evaluation of Medicines for Human Use

CHMP variation assessment report

Invented name/Name: Focetria
International non-proprietary name/Common name: pandemic influenza vaccine (surface antigen, inactivated, adjuvanted) a/california/7/2009 (h1n1)v like strain (x-181)

Type II Variation: EMEA/H/C/000710/II/0020

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

This type II variation relates to the following changes:

Update of section 4.2, 4.5, 4.8 and 5.1 of the SPC to include safety and immunogenicity information following assessment of the H1N1 data available with Focetria in children, adults and the elderly. The package leaflet is updated accordingly. Annex II is updated to reflect the fulfilment of Specific Obligations.

The following marketing authorisation holder's (MAH) specific obligations have been fulfilled:

Study V111_02 - post dose 1

Study V111_04 - post dose 2

Study V111_03:

Post dose 2 (3-17 years)

Post dose 1 (12-35 months)

Section 4.8 is also updated with regards to adverse drug reactions reported in the context of sPSUR4 (period covered 29 December to 25 January 2010).

1.2. Assessment

1.2.1. Introduction

Focetria is a pandemic H1N1v vaccine. The strain change of the mock-up vaccine from H5N1 to H1N1v was approved on 29/09/09 (EMEA/H/C/710/PU/05).

The current posology of Focetria was based on data from the mock-up vaccines, largely represented by vaccines containing the avian derived H5N1 antigen, scarcely immunogenic in humans. The current pandemic is caused by an A/H1N1 viral strain. The MAH is conducting a H1N1 clinical trial to assess the safety and efficacy of the vaccine in children, adults and the elderly.

Within this variation the MAH applied for a change in the posology for recommendation of a single dose in subjects 60-65 on the basis of study V111_02. The MAH also applied to amend section 4.5 with regards to concomitant administration of seasonal and pandemic vaccine on the basis of study V111_04. Section 4.8 is updated further to the evaluation of sPSUR 4 (29 December 2009 to 25 January 2010). Furthermore section 4.8 and 5.1 is updated with the available H1N1 data from study V111_03 in children.

The specific data sets will be discussed separately hereafter.

1.2.2. Clinical immunogenicity and safety

Study V111_02

Within this variation the MAH applied for a change in the posology for recommendation of a single dose in subjects 60-65.

In the context of variation EMEA/H/C/000710/II/0011 (commission decision 11 November 2009) it was agreed that one dose was sufficiently immunogenic in adults 18-60 years old as all three CHMP criteria were met in this age group after one dose. This was not the case in the elderly and the effect of the second dose was considered necessary in order to review the posology for this age group.

The present assessment is based on the available data at day 43 (i.e., 21 days after the second vaccination) from the Clinical Study V111_02.

In many EU countries seasonal influenza recommendations is offered to elderly population. The age cut-off used to identify elderly population is 65 years. This is not fully in agreement with the current recommendations of clinical trials for influenza which require that adults in the age groups 18-60 and above 60 years are separately investigated. In the current Focetria SmPC posology in adults 18-60 years (one dose) is different compared to the posology in subjects above 60 years of age (two doses).

Table 1: Overview of study V111_02

Study ID	Study Objectives	Study Design: Randomization Blinding	Number of Subjects Enrolled and Age Test Products: Dosage Regimen; Route of Administration
V111_02 Germany Belgium Switzerland 2009 a	Immunogenicity, and safety of different formulations of adjuvanted and non-adjuvanted egg-derived, inactivated novel swine origin A/H1N1 monovalent subunit influenza virus vaccine	Randomized, Single-blind, Dose-ranging	661 healthy subjects: 18-60 years >60 years 137 3.75_halfMF59 (0.25mL) 136 7.5_fullMF59 (0.5mL) 137 15µg_no MF59 (0.5mL) 126 3.75_halfMF59 (0.25mL) 125 7.5_fullMF59 (0.5mL) IMc

Results

A summary of immunogenicity data collected up to day 43 are presented hereafter. The CHMP criteria for the evaluation of pandemic vaccines were used to assess the immune response.

Subjects 18-60 years of age

Table 2: Immunogenicity up to post day 43 – adults 18-60 years

	Adults (18-60 years)			
Anti-HA antibody	21 days after 1st dose(day 22)		21 days after 2nd dose (day 43)	
	Total N=120	Seronegative at baseline N=46	Total N=120	Seronegative at baseline N=46
Seroprotection rate (95% CI)	96% (91-99)	98% (88-100)	100% (97-100)	100% (92-100)
GMR (95% CI)	17 (13-23)	44 (24-80)	23 (17-30)	75 (45-124)
Seroconversion or Significant Increase (95% CI)	88% (81-93)	98% (88-100)	95% (89-98)	100% (92-100)

* measured by HI assay
** geometric mean ratios of HI

Subjects 0ver 60 years of age

A summary of Immunogenicity data collected up to day 43 are presented hereafter. The CHMP criteria for the evaluation of pandemic vaccines were used to assess the immune response.

Table 3: Immunogenicity up to post day 43 – adults over 60 years

Anti-HA antibody	21 days after 1st dose(day 22)		21 days after 2nd dose (day 43)	
	Total N=117	Seronegative at baseline N=25	Total N=117	Seronegative at baseline N=25
Seroprotection rate (95% CI)	73% (64-80)	60% (39-79)	88% (81-93)	84% (64-95)
GMR (95% CI)	4.02 (3.1-5.2)	5.48 (2.82-11)	6.85 (5.36-8.75)	18 (8.9-35)
Seroconversion or Significant Increase (95% CI)	43% (34-52)	60% (39-79)	62% (53-71)	84% (64-95)

After the second vaccination there were further increases in GMTs of 10 to 23 fold from baseline in all vaccine groups, with the highest response being in the 7.5_full MF59 group.

The proportion of seroprotected subjects, among the 25 seronegative at baseline, after the first and the second dose is 60% (39%-79%) and 84% (64%-95%) respectively. Although the CIs overlap this is clearly due to the low sample size causing limited precision on the point estimates. In this situation the increase in proportion of seroprotected is considered relevant, pointing out the effect of the second dose.

Pair wise comparison of immune response at day 22 and at day 43 between vaccination groups indicated that the response to the 7.5_fullMF59 vaccination was higher than that to the 3.75_halfMF59 vaccination. The non-inferiority of 3.75 was not shown. The immune response is shown to be affected by previous seasonal flu, BMI, and age.

The current data do not modify the previous recommendation of administering one full dose in adults aged 18-60 years and two doses above 60 years of age.

Safety

The reactogenicity profile of all vaccines evaluated in this study was acceptable. In both age strata more subjects reported local reactions after adjuvanted vaccination compared with after unadjuvanted vaccination. The vast majority of solicited reactions were mild and self-limiting. Unsolicited AEs that were judged by the investigator to be at least possibly related to vaccination were balanced among the vaccine groups and caused by ongoing local and systemic reactions or other known side effects of vaccination. No deaths were reported until day 43. One subject (01/1028; renal colic) in 18 to 60 years old group and one subject (43/2004; worsening of right knee arthrosis) in over 60 years old group reported SAEs, which in the opinion of the investigator, were not related to the study vaccination. There was one premature withdrawal (51/1008 in adults 18-60 years group) and one premature withdrawal (41/2006 in adults over 60 years group) due to an AE. No pregnancies were reported during this study up to Day 43.

Conclusion Study V111_02

Although the data do not modify the posology recommendations, for public health purpose further consideration has been given to shifting the age cut-off of 60 years to include few additional years (up to 65 years) old subjects in order to match the current age groups in immunisation programs. For this purpose a subanalyses of study VIII-02 was submitted in which data were presented in 5-years age bands from 50 years onwards. The subanalyses included small numbers of subjects per age stratum. Although in the overall population and in the population with baseline titres <1:10 all 3 CHMP criteria were met for the 60-65 years cohort, this was not the case for the 50-55 and 55-60 years cohorts. This inconsistency does not support a change in dose recommendation.

The product information has been updated to reflect the post day 43 available safety and immunogenicity data from study V111_02.

Study V111_04

In this variation the MAH applied to update section 4.5 to specify that there is a lack of immunological interference of concomitant seasonal and pandemic vaccines on response to seasonal antigens, on the basis of study V111_04.

Study VIII_04 concerns the potential co-administration of Focetria with seasonal trivalent inactivated vaccines (TIV). This is a phase II comparative study conducted in 5 centers in Italy. Based on H5N1 data there was no indication of interference and thus co-administration was accepted in the SPC at the time of the authorization in 2009. However, the MAH was requested to investigate the potential interference of H1N1sv with TIV in study VIII_04. In the context of variation EMEA/H/C/000710/II/0013 in November 2009 the SPC was updated to indicate that concomitant administration of H1N1sv and TIV did not cause reduced immunologic response to pandemic antigens.

Study VIII_04 included individuals aged 18-60 and >60 years participating in trials for the 2008/2009 season (V71-10S and V70-09S) in which participants received either adjuvanted (Fluad) or nonadjuvanted (Agrippal) TIV and subsequently received H1N1sv vaccine in 2009. In addition the study enrolled individuals 18-60 years not yet exposed to the 2009-2010 seasonal vaccine. The MAH has presented the post dose 2, day 43 data. Since in Italy elderly are vaccinated with adjuvanted TIV (Fluad) no control group of unadjuvanted TIV co-administered with Focetria is presented.

Immunogenicity Results of Concomitantly Administered Single IM Seasonal TIV

GMTs and GMRs

GMR criterion met for each of the seasonal strains.

Table 4: GMTs and GMRs (95% CI) against the Seasonal Strains after TIV Vaccination in Adults 18 to 60 Years: PPS and HI Assay.

	A/Brisbane/59/2007 (H1N1)-like virus		A/Brisbane/10/2007 (H3N2)-like virus		B/Brisbane/60/2008-like virus	
	7.5_fullMF59 TIV N=67	+3.75_halfMF59 + TIV N=68	7.5_fullMF59 TIV N=67	+3.75_halfMF59 + TIV N=68	7.5_fullMF59 TIV N=67	+3.75_halfMF59 + TIV N=68
Day 1	27 (19-37)	28 (20-38)	24 (17-34)	29 (21-41)	12 (9.82-15)	15 (12-18)
Day 22	153 (117-199)	165 (127-214)	142 (106-190)	135 (101-180)	54 (43-68)	68 (54-86)
Day 22 over Day 1	5.69 (4.07-7.95)	5.92 (4.25-8.26)	5.96 (4.1-8.65)	4.64 (3.2-6.71)	4.41 (3.31-5.89)	4.66 (3.5-6.21)

Seroconversion

Seroconversion criterion met for each of the seasonal strains:

Table 5: Percentages (95%CI) of Adults Ages 18 to 60 Years with Seroconversion against the Seasonal Strains after TIV Vaccination: PPS and HI

	A/Brisbane/59/2007 (H1N1)-like virus		A/Brisbane/10/2007 (H3N2)-like virus		B/Brisbane/60/2008-like virus	
	7.5_full MF59 TIV	3.75_halfMF59 + TIV	7.5_full MF59 TIV	3.75_halfMF59 + TIV	7.5_full MF59 TIV	3.75_halfMF59 + TIV
	N=67	**N=68**	**N=67**	**N=68**	**N=67**	**N=68**
Day 22	57% (44%-69%)	65% (52%-76%)	55% (43%-67%)	51% (39%-64%)	57% (44%-69%)	59% (46%-71%)

Seroprotection

Seroprotection criterion met for each of the seasonal strains:

Table 6: Percentages (95%CI) of Adults Ages 18 to 60 Years with Seroprotection against the Seasonal Strains after TIV Vaccination: PPS and HI Assay

	A/Brisbane/59/2007 (H1N1)-like virus		A/Brisbane/10/2007 (H3N2)-like virus		B/Brisbane/60/2008-like virus	
	7.5_full MF59 TIV	3.75_halfMF59 + TIV	7.5_full MF59 TIV	3.75_halfMF59 + TIV	7.5_full MF59 TIV	3.75_halfMF59 + TIV
	N=67	**N=68**	**N=67**	**N=68**	**N=67**	**N=68**
Day 1	29 (43%) (31-56)	32 (47%) (35-60)	31 (46%) (34-59)	30 (44%) (32-57)	11 (16%) (8-27)	16 (24%) (14-35)
Day 22	62 (93%) (83-98)	65 (96%) (88-99)	57 (85%) (74-93)	63 (93%) (84-98)	53 (79%) (67-88)	56 (82%) (71-91)

Source: Table 14.2.1.1.4

Safety

Concomitant administration did not cause any increase in local and systemic reactogenicity.

Table 7: Numbers (%) of Subjects Reporting Solicited Local and Systematic Reactions after First and Second Vaccinations in Adults 18-60 years of Age: Safety Set

	TIV→ 7.5_full MF59	7.5_fullMF59	7.5_full MF59 + TIV	3.75_halfMF59 + TIV
First Vaccination	N=50	N=71	N=71	N=72
Any	32 (64%)	55 (77%)	51 (72%)	51 (71%)
Local	25 (50%)	43 (61%)	43 (61%)	41 (57%)
Systemic	23 (46%)	45 (63%)	36 (51%)	36 (50%)
Other*	2 (4%)	11 (15%)	6 (8%)	9 (13%)
Second Vaccination	N=50	N=71	N=70	N=69
Any	24 (48%)	53 (75%)	48 (69%)	37 (54%)
Local	18 (36%)	43 (61%)	38 (54%)	28 (41%)
Systemic	15 (30%)	36 (51%)	32 (46%)	26 (38%)
Other*	4 (8%)	6 (8%)	6 (9%)	8 (12%)

Source: Table 14.3.1.1.2.2, *Other= Analgesic and/or antipyretics use

Table 8: Numbers (%) of Subjects Reporting All unsolicited AEs after First and Second Vaccinations in Adults 18-60 years of Age: Safety Set

	TIV→ 7.5_fullMF59	7.5_fullMF59	7.5_fullMF59 + TIV	3.75_halfMF59 + TIV
	N=50	N=71	N=71	N=72
Any AE	8 (16%)	27(38%)	28 (39%)	34 (47%)
Possibly/Prob. Related AE	2 (4%)	3 (4%)	5 (7%)	4 (6%)
Any SAE	0	0	0	1 (1%)
Possibly/Prob Related SAEs	0	0	0	0
AE leading to withdrawal	0	0	0	1 (1%)

Source: Table 14.3.1.1.7.3; Table 14.3.1.1.7.1; Table 14.3.1.1.15.1; Table 14.3.1.12.1; Table 14.3.2.3;

Conclusion concerning Concomitant administration

The data presented support the previous recommendation that Focetria may be co-administered with non adjuvanted seasonal influenza vaccine. However the MAH did not compare directly the immune response to seasonal vaccine with or without concomitant pandemic vaccination. Therefore the statement that no interference is made to seasonal antigens has not been agreed by CHMP. However considering the usefulness of co-administartion in adults >60 years an additional statement has been added at the beginning of the relevant paragraph that Focetria may be co-administered with a non-adjuvanted seasonal vaccine.

Study V111_03

The study assesses the preferable vaccine formulation, antigen and adjuvant dose, and schedule in the age group 6 months 17 years. The effect of two doses of Focetria administered with an interval of

three weeks in paediatric population is assessed. In the protocol the effect of a booster dose 12 months apart from the first two administrations has also been included.

The CHMP has assesed the available data available up to the Abridged Study Report at day 43 for cohorts 1 and 2 on children 3-17 years old, provided on 29 January 2010 and Interim data at day 22 on children in the cohort 3. Assessment of the data and considerations of the impact of the data on the posology are being made in parallel in variation EMEA/H/C/000710/II/0019.

In order to make available in the SPC the latest H1N1 data in pediatrics section 4.1, 4.8 and 5.1 of the SPC have been updated with data from Study V1111_03.

A summary of available immunogenicity data up to post day 43 for children 3-17 years old are presented hereafter:

Table 9: Immunogenicity post day 43 – children 9-17 years

	Children and Adolescents (9-17 years)			
Anti-HA antibody	21 days after 1st dose(day 22)		21 days after 2nd dose (day 43)	
	Total N=88	Seronegative at baseline N=51	Total N=88	Seronegative at baseline N=51
Seroprotection rate (95% CI)	97% (90-99)	94% (84-99)	99% (94-100)	98% (90-100)
GMR (95% CI)	62 (38-100)	102 (60-170)	83 (54-127)	169 (122-235)
Seroconversion or Significant Increase (95% CI)	94% (87-98)	94% (84-99)	94% (87-98)	98% (90-100)

* measured by HI assay
** geometric mean ratios of HI
^ Additional data will become available from the same study.

Table 10: Immunogenicity post day 43 – children 3-8 years

	Children (3-8 years)			
Anti-HA antibody	21 days after 1st dose(day 22)		21 days after 2nd dose (day 43)	
	Total N=70	Seronegative at baseline N=48	Total N=70	Seronegative at baseline N=48
Seroprotection rate (95% CI)	100% (95-100)	100% (93-100)	100% (95-100)	100% (93-100)
GMR (95% CI)	37 (25-55)	50 (32-76)	81 (52-125)	146 (100-212)
Seroconversion or Significant Increase (95% CI)	99% (92-100)	100% (93-100)	99% (92-100)	100% (93-100)

A summary of available immunogenicity data up to post day 22 for children 12 – 35 months old are presented hereafter:

Table 11: Immunogenicity Data on post day 22 for children 12-35 months

Anti-HA antibody	Children (12-35 months)	
	Total N=80	Seronegative at baseline N=53
Seroprotection rate (Day 22)	99% (95%CI: 93-100)	100% (95%CI: 93-100)
GMR (Day 22 to Day 1)	29 (95%CI: 17-50)	47 (95%CI: 30-75)

Seroconversion or Significant Increase (Day 22)	96% (95%CI: 89-99)	100% (95%CI: 93-100)

The ongoing parallel variation EMA/H/C/00710/II/0019 is assessing study V111_03 with a view to establishing any impact on posology.

Safety

In children and adolascents 3-17 years of age sfatey data up to day 43 are now available and suggest a comparable sfatey profile with that reported so far and for the H5N1 mock up vaccine formulaiton.

Post day 22 data from 81 children 12-35 months old receiving the 7.5 µg formulation, are now available and showed that during the week following the first vaccination 68% of subjects reported at least one adverse reaction of any type, 49% of the subjects reported local reactions at the injection site, and 53% of the subjects reported systemic reactions.

Very common reactions reported in children 12 to 35 months of age included tenderness, induration and erythema, irritability, unusual crying, sleepiness, diarrhoea and change in eating habits. Fever (≥38°C) has been reported by 14% of subjects 12-35 months old with one subject (1%) reporting fever ≥40°C.

Conclusion V111_03

Currently available safety and immunogenicity H1N1 data has been reflected in the product information. The ongoing parallel variation EMA/H/C/00710/II/0019 is assessing this data with a view to establishing any impact on posology.

Safety – sPSUR

Further to the assessment of sPSUR 4 the following Adverse Drug Reactions were identified for inclusion in section 4.8 of the SPC, as reported in the post marketing setting.

Table 12: Cumulative list of ADRs up to sPSUR 4

SOC	Preferred Term	Cumulative number of ADRs from PSUR 4
General disorders and administration site conditions:	asthenia	131 (122 mc + 9 ncm∗)
Muscoloskeletal, connective tissue and bone disorders	Pain in the extremity:	194 (168 mc+26nmc)
	Muscular weakness	59 (54 mc+5nmc)
Gastrointestinal disorders	Abdominal pain	108 (101 mc+7 nmc)
Respiratory, thoracic and mediastinal disorders	cough	223 (192 mc+31 nmc)
Cardiac disorders	tachycardia	37 (30 mc+7 nmc)
	palpitations:	55 (52mc+3nmc)
Blood and lymphatic system disorders	lymphadenopathy	79 (77mc +2 nmc)

∗ nmc = non-medically confirmed

1.3. Changes to the product Information

The proposed changes to section 4.2, 4.4, 4.8 and 5.1 of the SPC were reviewed and initially not agreed with. A revision of the wording was submitted taking into account the results of the assessment

and this was agreed with by the CHMP. The PL was updated accordingly. Annex II was amended to reflect the fulfilment of specific obligations:

Study V111_02 post dose 2

Study V111_04 post dose 2

Study V111_03:

- Post dose 2 Cohort 1 and 2
- Post dose 1 Cohort 3

Of note study V111_03 is assessed in parallel in Variation II 19. It has been agreed that post dose 2 cohort 3 (children 12-35 months) will be submitted on 26 February to allow parallel assessment with post dose 1 cohort 4 (children 6-11 months). This has been reflected in Annex II.

1.4. Overall discussion and benefit risk assessment

Regarding study V111_02, the data post dose 43 do not allow to modify the previous recommendations of administering one full dose in adults aged 18-60 and two full doses above 60. The subanayses provided included small numbers of subjects per age stratum. Although in the overall population and in the population with baseline titres <1:10 all 3 CHMP criteria are met for the 60-65 years cohort, this was not the case for the 50-55 and 55-60 years cohorts. This inconsistency does not support a change in dose recommendation.

Regarding study V111_04 all data presented support the previous observation that Focetria may be co-administered with non adjuvanted seasonal influenza vaccine. However the MAH did not compare directly the immune response to seasonal vaccine with or without concomitant pandemic vaccination. Therefore the staement that no interference is made to seasonal antigens has not been agreed by CHMP. However considering the usefulness of co-administartion in adults >60 years an additional statement has been added at the beginning of the relevant paragraph that Focetria may be co-administered with a non-adjuvanted seasonal vaccine.

Regarding study V111-03, currently available safety and immunogenicity data from post dose 2 in children 3-17 years and post dose 1 in children 12-35 months has been included in the SPC. Assessment of study V111_03 with a view to establishing any impact on posology are made in parallel in the context of varaition II 19.

Adverse drug reactions identified during the assessment of sPSUR 4 has been included in the product information.