

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Focetria suspension for injection in pre-filled syringe
Pandemic influenza vaccine (surface antigen, inactivated, adjuvanted)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Influenza virus surface antigens (haemagglutinin and neuraminidase)* of strain:

A/California/7/2009 (H1N1)v like strain (X-181)	7.5 micrograms** per 0.5 ml dose
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* propagated in eggs

** expressed in microgram haemagglutinin.

Adjuvant MF59C.1 containing:

squalene	9.75 milligrams
polysorbate 80	1.175 milligrams
sorbitan trioleate	1.175 milligrams

This vaccine complies with the WHO recommendations and EU decision for the pandemic.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in pre-filled syringe.
Milky-white liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of influenza in an officially declared pandemic situation (see sections 4.2 and 5.1).
Pandemic influenza vaccine should be used in accordance with Official Guidance.

4.2 Posology and method of administration

The dose recommendations take into account available data from on-going clinical studies in healthy subjects most of whom received a single dose of Focetria (H1N1) and from clinical studies in healthy subjects who received two doses of a version of Focetria containing HA derived from A/Vietnam/1194/2004 (H5N1).

In some age groups there are limited data (adults above 60 years of age) or no data (children aged less than 6 months) with one or both versions of Focetria as detailed in sections 4.8 and 5.1.

Posology:

Adults (18-60 years):

One dose of 0.5 ml at an elected date.

Immunogenicity data obtained at three weeks after administration of Focetria (H1N1) in clinical studies suggest that a single dose may be sufficient.

If a second dose is administered there should be an interval of at least three weeks between the first and second dose.

Elderly (>60 years):

One dose of 0.5 ml at an elected date.

A second dose of vaccine should be given after an interval of at least three weeks. See section 5.1.

Children and adolescents aged 9-17 years:

One dose of 0.5 ml at an elected date.

Immunogenicity data obtained at three weeks after administration of Focetria in clinical studies suggest that a single dose may be sufficient. If a second dose is administered there should be an interval of at least three weeks between the first and second dose.

Children aged 3-8 years:

One dose of 0.5 ml at an elected date.

Immunogenicity data show that there is a further immune response to a second dose of 0.5 ml administered after an interval of three weeks.

The use of a second dose should take into consideration the information provided in section 5.1.

Children aged 6 months to 35 months:

One dose of 0.5 ml at an elected date.

A second dose of vaccine should be given after an interval of at least three weeks.

Children aged less than 6 months:

Vaccination is not currently recommended in this age group.

It is recommended that subjects who receive a first dose of Focetria, should complete the vaccination course with Focetria (see section 4.4).

Method of administration

Immunisation should be carried out by intramuscular injection preferably into the deltoid muscle or anterolateral thigh (depending on the muscle mass).

4.3 Contraindications

History of an anaphylactic (i.e. life-threatening) reaction to any of the constituents or trace residues (egg and chicken proteins, ovalbumin, kanamycin and neomycin sulphate, formaldehyde and cetyltrimethylammonium bromide (CTAB)) of this vaccine. If vaccination is considered to be necessary, facilities for resuscitation should be immediately available in case of need.

See section 4.4 for Special warnings and special precautions for use.

4.4 Special warnings and precautions for use

Caution is needed when administering this vaccine to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance, to any of the excipients and to residues (eggs and chicken protein, ovalbumin, kanamycin and neomycin sulphate, formaldehyde and cetyltrimethylammonium bromide (CTAB)).

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

If the pandemic situation allows, immunisation should be postponed in patients with severe febrile illness or acute infection.

Focetria should under no circumstances be administered intravascularly.

There are no data with Focetria using the subcutaneous route. Therefore, healthcare providers need to assess the benefits and potential risks of administering the vaccine in individuals with thrombocytopenia or any

bleeding disorder that would contraindicate intramuscular injection unless the potential benefit outweighs the risk of bleedings.

Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.

A protective response may not be elicited in all vaccinees (see section 5.1).

In the event that a second dose is to be administered it should be noted that there are no safety, immunogenicity or efficacy data to support interchangeability of Focetria with other H1N1 pandemic vaccines.

4.5 Interaction with other medicinal products and other forms of interaction

Focetria (H1N1) may be co-administered with a non adjuvanted seasonal influenza vaccine. Data on co-administration of Focetria (H1N1) with a non-adjuvanted seasonal influenza subunit vaccine in healthy adults aged 18-60 years of age did not suggest any interference in the immune response to Focetria. The immune response to the seasonal antigens was satisfactory.

Co-administration was not associated with higher rates of local or systemic reactions compared to administration of Focetria alone.

The same study demonstrated that previous administration of adjuvanted or unadjuvanted seasonal influenza vaccines to adults and elderly does not interfere with the immune response to Focetria.

Therefore the data indicate that Focetria may be co-administered with non adjuvanted seasonal influenza vaccines (with injections made into opposite limbs).

There are no data on co-administration of Focetria with other vaccines.

If co-administration with another vaccine is considered, immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

Following influenza vaccination, false positive serology test results may be obtained by the ELISA method for antibody to human immunodeficiency virus-1 (HIV-1), hepatitis C virus and, especially, HTLV-1. In such cases, the Western Blot method is negative. These transitory false positive results may be due to IgM production in response to the vaccine.

4.6 Pregnancy and lactation

There are currently no data available on the use of Focetria in pregnancy. Data from pregnant women vaccinated with different inactivated non-adjuvanted seasonal vaccines do not suggest malformations or fetal or neonatal toxicity.

An animal study with H5N1 mock-up vaccine did not indicate reproductive toxicity (see section 5.3).

The use of Focetria may be considered during pregnancy if this is thought to be necessary, taking into account official recommendations.

Focetria may be used in lactating women.

4.7 Effects on ability to drive and use machines

Some of the effects mentioned under section 4.8 “Undesirable Effects” may affect the ability to drive or use machines.

4.8 Undesirable effects

- Clinical trials

Adverse reactions reported are listed according to the following frequency:

Very common ($\geq 1/10$),

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$),
Rare ($\geq 1/10,000$ to $< 1/1,000$),
Very rare ($< 1/10,000$).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:

Adult and Elderly

In an ongoing clinical trial 131 adults and 123 elderly were exposed to two doses of the 7.5 µg Focetria (H1N1) pandemic vaccine. The safety profile of Focetria was similar to that of the H5N1 mock up vaccines. Most of the reactions were mild in nature and of short duration. The incidence of symptoms observed in subjects over 60 years of age was generally lower as compared to the 18-60 years old population.

Very common: pain, induration and erythema, myalgia, headache, sweating, malaise and fatigue

In clinical trials with different formulations (H5N3, H9N2 and H5N1) approximately 3400 subjects were exposed to the mock-up vaccines.

Most of the reactions were mild in nature, of short duration and qualitatively similar to those induced by conventional seasonal influenza vaccines. It is widely accepted that the adjuvant effect leading to increased immunogenicity is associated with a slightly higher frequency of local reactions (mostly mild pain) compared with conventional, nonadjuvanted influenza vaccines. There were fewer reactions after the second vaccination compared with the first.

Adverse reactions from clinical trials with the mock-up vaccine are listed below (see section 5.1 for more information on mock-up vaccines and Focetria).

The incidence of symptoms observed in subjects over 60 years of age was lower as compared to the 18-60 years old population.

Nervous system disorders

Very common: headache
Rare: convulsions

Skin and subcutaneous tissue disorders

Common: sweating
Uncommon: urticaria
Rare: eye swelling

Musculoskeletal, connective tissue and bone disorders

Very common: myalgia
Common: arthralgia

Gastrointestinal disorders

Common: nausea

General disorders and administration site conditions

Very common: injection site swelling, injection site pain, injection site induration, injection site redness, fatigue, malaise and shivering
Common: injection site ecchymosis and fever
Uncommon: influenza like illness
Rare: anaphylaxis
The common reactions usually disappear within 1-2 days without treatment.

Children and adolescents 6 months to 17 years of age

Clinical trials with Focetria (H1N1)

Safety data after the first and second dose in children and adolescents suggest a comparable safety profile with that reported for the H5N1 mock-up vaccine formulation.

Adverse reactions in the week following vaccination from 87 children 3-8 years old and 95 children and adolescents 9-17 years old receiving the 7.5 µg formulation were reported as follows:

	Injection 1	Injection 2
Children (3 to 8 years of age)	N=87	N=85
Any averse reaction	67%	61%
Local	56%	49%
Systemic	32%	31%
Fever $\geq 38^{\circ}\text{C}/\geq 39^{\circ}\text{C}/\geq 40^{\circ}\text{C}$	3% / 0% / 0%	1% / 1% / 0%
Any other AE	13%	15%
Adolescents (9 to 17 years of age)	N=95	N=94
Any averse reaction	67%	55%
Local	60%	49%
Systemic	38%	26%
Fever $\geq 38^{\circ}\text{C}/\geq 39^{\circ}\text{C}/\geq 40^{\circ}\text{C}$	2% / 0% / 0%	1% / 0% / 0%
Any other AE	11%	9%

Data in children and adolescents 3-17 years suggest a slight decrease in reactogenicity after the second dose, with no increase in rates of fever.

Very common reactions reported in children and adolescents 3 to 17 years of age:

Pain, induration and erythema, malaise, myalgia, headache and fatigue.

Data from 81 children 12-35 months old receiving the 7.5 µg formulation, 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:

Tenderness, induration and erythema, irritability, unusual crying, sleepiness, diarrhoea and change in eating habits.

Fever ($\geq 38^{\circ}\text{C}$) has been reported by 14% of subjects 12-35 months old with one subject (1%) reporting fever $\geq 40^{\circ}\text{C}$.

Clinical trials with the H5N1 Mock-up vaccine

A clinical trial was conducted with a H5N1 vaccine combined with MF59C.1 adjuvant in 471 children from 6 months to 17 years of age. Two doses of vaccine containing H5N1 (A/Vietnam/1194/2004) at the dosage of 7.5 µg hemagglutinin [HA]/dose with MF59C.1 adjuvant were administered three weeks apart. The effect of the administration of a booster dose 12 months following the second dose has also been evaluated.

Local and systemic reactogenicity was monitored for the week following vaccine administration. Local reactions were more frequent at subsequent administrations following the first one, at any age.

Most systemic reactions were experienced within 3 days following vaccination and were transient and mild of moderate severity.

In these age groups, the per-dose frequency of reactions was higher than the one reported for adults and elderly. A higher frequency of fever $>39.0^{\circ}\text{C}$ was also observed.

Systemic adverse events reported very commonly in the 6 months-35 months of age group per dose were irritability, unusual crying, sleepiness, diarrhoea and change in eating habits. In children very common systemic events included headache, fatigue. Among the adolescents the very common events were: malaise, myalgia, headache, fatigue, sweating, nausea, chills.

Percentages of subjects with solicited and unsolicited reactions are provided below:

	Injection 1	Injection 2
Toddlers (6 to 35 months)	N=145	N=138
Local	47%	46%
Systemic	59%	51%
Fever $\geq 38^{\circ}\text{C}/\geq 39^{\circ}\text{C}/\geq 40^{\circ}\text{C}$	7% / 1% / 0%	12% / 3% / 0%
Any other AE	54%	49%
Children (3 to 8 years of age)	N=96	N=93
Local	66%	58%
Systemic	32%	33%
Fever $\geq 38^{\circ}\text{C}/\geq 39^{\circ}\text{C}/\geq 40^{\circ}\text{C}$	4% / 1% / 0%	2% / 0% / 0%
Any other AE	36%	31%
Adolescents (9 to 17 years of age)	N=93	N=91
Local	81%	70%
Systemic	69%	52%
Fever $\geq 38^{\circ}\text{C}/\geq 39^{\circ}\text{C}/\geq 40^{\circ}\text{C}$	0% / 0% / 0%	1% / 0% / 0%
Any other AE	30%	27%

- Post-marketing surveillance

Focetria (H1N1)

In addition to the adverse reactions reported in the clinical trials, the following have been reported during post-marketing experience with Focetria H1N1:

Blood and lymphatic system disorders

Lymphadenopathy.

Cardiac disorders

Palpitation, tachycardia.

General disorders and administration site conditions

Asthenia.

Musculoskeletal, connective tissue and bone disorders

Muscular weakness, pain in extremities.

Respiratory disorders

Cough.

Skin and subcutaneous tissue disorders

Generalised skin reactions including pruritus, urticaria or non-specific rash; angioedema.

Gastrointestinal disorders

Gastrointestinal disorders such as nausea, vomiting, abdominal pain and diarrhoea.

Nervous system disorders

Headache, dizziness, somnolence, syncope. Neurological disorders, such as neuralgia, paraesthesia, convulsions and neuritis.

Immune system disorders

Allergic reactions, anaphylaxis including dyspnoea, bronchospasm, laryngeal oedema, in rare cases leading to shock.

In addition, from Post-marketing surveillance with seasonal trivalent vaccines in all age groups and with the MF59 adjuvanted seasonal trivalent vaccine with the similar composition of Focetria (surface antigen, inactivated, adjuvanted with MF59C.1), licensed for use in elderly subjects above 65 years of age, the following adverse events have been reported:

Rare:

Transient thrombocytopenia.

Very rare:

Vasculitis with transient renal involvement and exudative erythema multiforme.
Neurological disorders, such as encephalomyelitis and Guillain Barré syndrome.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccine, ATC Code: J07BB02

This medicinal product has been authorised under “Exceptional Circumstances”.

The European Medicines Agency (EMA) will regularly review any new information which may become available and this SPC will be updated as necessary.

Mock-up vaccines contain influenza antigens that are different from those in the currently circulating influenza viruses. These antigens can be considered as ‘novel’ antigens and simulate a situation where the target population for vaccination is immunologically naïve. Data obtained with a mock-up vaccine will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical immunogenicity, safety and reactogenicity data obtained with mock-up vaccines are relevant for the pandemic vaccines.

Clinical studies with Focetria (H1N1) currently provide:

- Available safety and immunogenicity data obtained after administration of one or two doses of Focetria (H1N1) to healthy children and adolescents aged 3-17 years and to healthy adults, including the elderly.

Clinical studies in which a version of Focetria containing HA derived from A/Vietnam/1194/2004 (H5N1) was administered at day 1 and at day 22 provide:

- Safety and immunogenicity data in healthy children and adolescents aged from 6 months to 17 years and in adults, including the elderly

Immune response to Focetria (H1N1)

- Studies in adults and elderly:

Immunogenicity results with two doses of 7.5 µg Focetria (H1N1) pandemic vaccine from the ongoing clinical trial in adults and elderly are shown below.

The seroprotection rate*, seroconversion rate* and the seroconversion factor ** for anti-HA antibody to A/H1N1 in adult and elderly subjects by HI assay after administration of 7.5 µg of Focetria were as follows:

	Adults (18-60 years)			
Anti-HA antibody	21 days after 1 st dose(day 22)		21 days after 2 nd 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

	Elderly (>60 years)			
Anti-HA antibody	21 days after 1 st dose(day 22)		21 days after 2 nd 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)

- Studies in children

The seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibody to H1N1 in children and adolescents aged 9-17 years by HI assay after administration of 7.5 µg of Focetria were as follows:

	Children and Adolescents (9-17 years)			
Anti-HA antibody	21 days after 1 st dose(day 22)		21 days after 2 nd 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.

Data on responses to a second dose administered after an interval of three weeks showed an increase in overall GMT from 793 to 1065 (N=88) and an increase in GMT from 522 to 870 in children who were seronegative at baseline (N=51).

The seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibody to H1N1 in children aged 3-8 years by HI assay after administration of 7.5 µg of Focetria were as follows:

Anti-HA antibody	Children (3-8 years)			
	21 days after 1 st dose(day 22)		21 days after 2 nd 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)

Data on responses to a second dose administered after an interval of three weeks showed an increase in overall GMT from 319 to 702 (N=70) and an increase in GMT from 247 to 726 in children who were seronegative at baseline (N=48).

The seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibody to H1N1 in children aged 12-35 months by HI assay after a single dose of 7.5 µg of Focetria were as follows:

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)

Limited data available on responses to a second dose administered after an interval of three weeks showed an increase in overall GMT from 333 to 976 (N=871) and an increase in GMT from 237 to 776 in children who were seronegative at baseline (N=46).

Immune response to mock-up H5N1 vaccine:

- Studies in adults and elderly

A clinical trial was conducted with a H5N1 vaccine combined with MF59C.1 adjuvant in 486 healthy adult volunteers. Two doses of vaccine containing H5N1 (A/Vietnam/1194/2004) (7.5 µg hemagglutinin [HA]/dose) with MF59C.1 adjuvant were administered three weeks apart.

The seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibody to H5N1 A/Vietnam/1194/2004 in the adults measured by SRH were as follows:

Anti-HA antibody	21 days after 1 st dose	21 days after 2 nd dose
Seroprotection rate	41% (95% CI: 33-49)	86% (95% CI: 79-91)
Seroconversion rate	39% (95% CI: 31-47)	85% (95% CI: 79-91)
Seroconversion factor	2.42 (2.02-2.89)	7.85 (6.7-9.2)

* measured by SRH assay $\geq 25 \text{ mm}^2$

** geometric mean ratios of SRH

The seroprotection rate*, seroconversion rate* and the seroconversion factor ** for anti-HA antibody to H5N1 A/Vietnam/1194/2004 in subjects aged over 60 measured by SRH were as follows:

Anti-HA antibody	21 days after 1 st dose	21 days after 2 nd dose
Seroprotection rate	53% (95% CI: 42-64)	81% (95% CI: 71-89)
Seroconversion rate	45% (95% CI: 34-56)	71% (95% CI: 60-81)
Seroconversion factor	2.85 (2.22-3.66)	5.02 (3.91-6.45)

* measured by SRH assay $\geq 25 \text{ mm}^2$

** geometric mean ratios of SRH

Limited data on the persistence of antibodies in elderly immunised with the H5N1 mock-up vaccine showed that up to 50% of the subjects were seroprotected at six months.

Cross-reactivity of highly pathogenic variants of A/Vietnam/1194/2004 (H5N1) in subjects 18 years and above.

Immunogenicity analyses were carried out for influenza A/H5N1/turkey/Turkey/05 (NIBRG23; clade 2.2) with HI, SRH, and MN and for influenza A/H5N1/Indonesia (clade 2.1) with HI and MN, on sera collected 3 weeks after the second vaccination (day 43) and 3 weeks after the booster vaccination (day 223).

In both age groups the responses to the heterologous strains highly increased after booster vaccination with the mock-up vaccine by all assays used.

- Studies in children

A clinical trial was conducted with a H5N1 vaccine combined with MF59C.1 adjuvant in 471 children from 6 months to 17 years of age. Two doses of vaccine containing H5N1 (A/Vietnam/1194/2004) at the dosage of 7.5 μg hemagglutinin [HA]/dose with MF59C.1 adjuvant were administered three weeks apart.

The seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibody to H5N1 A/Vietnam/1194/2004 in the toddlers aged from 6 to 35 months measured by SRH were as follows:

Anti-HA antibody	21 days after 1 st dose	21 days after 2 nd dose
Seroprotection rate	47% (CI: 38-55)	100% (CI: 97-100)
Seroconversion rate	44% (CI: 36-53)	98% (CI: 95-100)
Seroconversion factor	2.67 (2.24-3.18)	16 (14-18)

* measured by SRH assay $\geq 25 \text{ mm}^2$

** geometric mean ratios of SRH

The seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibody to H5N1 A/Vietnam/1194/2004 in the children aged from 3 to 8 years measured by SRH were as follows:

Anti-HA antibody	21 days after 1 st dose	21 days after 2 nd dose
Seroprotection rate	54% (CI: 44-65)	100% (CI: 96-100)
Seroconversion rate	56% (CI: 45-66)	100% (CI: 96-100)
Seroconversion factor	3.34 (2.74-4.06)	15 (13-17)

* measured by SRH assay $\geq 25 \text{ mm}^2$

** geometric mean ratios of SRH

The seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibody to H5N1 A/Vietnam/1194/2004 in the adolescent aged from 9 to 17 years measured by SRH were as follows:

Anti-HA antibody	21 days after 1 st dose	21 days after 2 nd dose
Seroprotection rate	59%(CI: 48-69)	100% (CI: 96-100)
Seroconversion rate	57% (CI: 46-67)	99% (CI: 94-100)
Seroconversion factor	3.87 (3.25-4.61)	14 (12-16)

* measured by SRH assay $\geq 25 \text{ mm}^2$

** geometric mean ratios of SRH

- Supportive Studies

In two dose finding studies 78 adults received an adjuvanted mock-up vaccine (H5N3 or H9N2).

Two doses of vaccine with H5N3 (A/Duck/Singapore/97) strain at 3 different dosages (7.5, 15 and 30 μg HA/dose) were administered three weeks apart.

Serum samples were tested against the original H5N3 and also a number of H5N1 isolates.

Serologic responses obtained with the SRH assay showed that 100% of subjects achieved seroprotection and 100% seroconverted after two 7.5 μg injections. The adjuvanted vaccine was also found to induce antibodies that cross-protected against the H5N1 strains isolated in 2003 and 2004, which exhibit some antigenic drift compared to the original strains.

Two doses of vaccine containing H9N2 (A/chicken/Hong Kong/G9/97) strain at 4 different dosages (3.75, 7.5, 15 and 30 μg HA/dose), were administered four weeks apart. Serologic responses obtained with the Hemagglutination Inhibition (HI) assay showed that 92% of subjects achieved seroprotection and 75% seroconverted after two 7.5 μg injections.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data obtained with the mock-up vaccine (MF59C.1-adjuvanted H5N1 vaccine) and with seasonal vaccine containing MF59C.1 adjuvant reveal no special hazard for humans based on conventional studies of efficacy, repeated dose toxicity, and reproductive and developmental toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride,
Potassium chloride,
Potassium dihydrogen phosphate,
Disodium phosphate dihydrate,
Magnesium chloride hexahydrate,
Calcium chloride dihydrate,
Sodium citrate,
Citric acid,
Water for injections.

For the adjuvant, see section 2.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

1 year.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze. Store in the original package in order to protect from light.

6.5 Nature and contents of container

0.5 ml in pre-filled syringe (type I glass) with plunger-stopper (bromo-butyl rubber). Packs of 1 and 10.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The vaccine should be allowed to reach room temperature before use. Gently shake before use. Any unused vaccine or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Vaccines and Diagnostics S.r.l. - Via Fiorentina, 1 – Siena, Italy.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/385/001

EU/1/07/385/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 May 2007

10. DATE OF REVISION OF THE TEXT

02/2010

Detailed information on this product is available on the website of the European Medicines Agency (EMA): <http://www.ema.europa.eu/>.

1. NAME OF THE MEDICINAL PRODUCT

Focetria suspension for injection in multidose container
Pandemic influenza vaccine (surface antigen, inactivated, adjuvanted)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Influenza virus surface antigens (haemagglutinin and neuraminidase)* of strain:

A/California/7/2009 (H1N1)v like strain (X-181) 7.5 micrograms ** per 0.5 ml dose

* propagated in eggs

** expressed in microgram haemagglutinin.

Adjuvant MF59C.1 containing:

squalene	9.75 milligrams
polysorbate 80	1.175 milligrams
sorbitan trioleate	1.175 milligrams

Excipients:

thiomersal	0.05 milligrams
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This vaccine complies with the WHO recommendations and EU decision for the pandemic.

This is a multidose container.

See section 6.5 for the number of doses per vial.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

Milky-white liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of influenza in an officially declared pandemic situation (see sections 4.2 and 5.1).

Pandemic influenza vaccine should be used in accordance with Official Guidance.

4.2 Posology and method of administration

The dose recommendations take into account available data from on-going clinical studies in healthy subjects most of whom received a single dose of Focetria (H1N1) and from clinical studies in healthy subjects who received two doses of a version of Focetria containing HA derived from A/Vietnam/1194/2004 (H5N1).

In some age groups there are limited data (adults above 60 years of age) or no data (children aged less than 6 months) with one or both versions of Focetria as detailed in sections 4.8 and 5.1.

Posology:

Adults (18-60 years):

One dose of 0.5 ml at an elected date.

Immunogenicity data obtained at three weeks after administration of Focetria (H1N1) in clinical studies suggest that a single dose may be sufficient.

If a second dose is administered there should be an interval of at least three weeks between the first and second dose.

Elderly (>60 years):

One dose of 0.5 ml at an elected date.

A second dose of vaccine should be given after an interval of at least three weeks. See section 5.1.

Children and adolescents aged 9-17 years:

One dose of 0.5 ml at an elected date.

Immunogenicity data obtained at three weeks after administration of Focetria in clinical studies suggest that a single dose may be sufficient. If a second dose is administered there should be an interval of at least three weeks between the first and second dose.

Children aged 3-8 years:

One dose of 0.5 ml at an elected date.

Immunogenicity data show that there is a further immune response to a second dose of 0.5 ml administered after an interval of three weeks.

The use of a second dose should take into consideration the information provided in section 5.1.

Children aged 6 months to 35 months:

One dose of 0.5 ml at an elected date.

A second dose of vaccine should be given after an interval of at least three weeks.

Children aged less than 6 months:

Vaccination is not currently recommended in this age group.

It is recommended that subjects who receive a first dose of Focetria, should complete the vaccination course with Focetria (see section 4.4).

Method of administration

Immunisation should be carried out by intramuscular injection preferably into the deltoid muscle or anterolateral thigh (depending on the muscle mass).

4.3 Contraindications

History of an anaphylactic (i.e. life-threatening) reaction to any of the constituents or trace residues (egg and chicken proteins, ovalbumin, kanamycin and neomycin sulphate, formaldehyde and cetyltrimethylammonium bromide (CTAB)) of this vaccine. If vaccination is considered to be necessary, facilities for resuscitation should be immediately available in case of need.

See section 4.4. for Special warnings and special precautions for use.

4.4 Special warnings and precautions for use

Caution is needed when administering this vaccine to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance, to any of the excipients, to thiomersal and to residues (eggs and chicken protein, ovalbumin, kanamycin and neomycin sulphate, formaldehyde and cetyltrimethylammonium bromide (CTAB)).

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

If the pandemic situation allows, immunisation should be postponed in patients with severe febrile illness or acute infection.

Focetria should under no circumstances be administered intravascularly.

There are no data with Focetria using the subcutaneous route. Therefore, healthcare providers need to assess the benefits and potential risks of administering the vaccine in individuals with thrombocytopenia or any bleeding disorder that would contraindicate intramuscular injection unless the potential benefit outweighs the risk of bleedings.

Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.

A protective response may not be elicited in all vaccinees (see section 5.1).

In the event that a second dose is to be administered it should be noted that there are no safety, immunogenicity or efficacy data to support interchangeability of Focetria with other H1N1 pandemic vaccines.

4.5 Interaction with other medicinal products and other forms of interaction

Focetria (H1N1) may be co-administered with a non adjuvanted seasonal influenza vaccine. Data on co-administration of Focetria (H1N1) with a non-adjuvanted seasonal influenza subunit vaccine in healthy adults aged 18-60 years of age did not suggest any interference in the immune response to Focetria. The immune response to the seasonal antigens was satisfactory.

Co-administration was not associated with higher rates of local or systemic reactions compared to administration of Focetria alone.

The same study demonstrated that previous administration of adjuvanted or unadjuvanted seasonal influenza vaccines to adults and elderly does not interfere with the immune response to Focetria.

Therefore the data indicate that Focetria may be co-administered with non adjuvanted seasonal influenza vaccines (with injections made into opposite limbs).

There are no data on co-administration of Focetria with other vaccines.

If co-administration with another vaccine is indicated, immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

Following influenza vaccination, false positive serology test results may be obtained by the ELISA method for antibody to human immunodeficiency virus-1(HIV-1), hepatitis C virus and, especially, HTLV-1 have been observed. In such cases, the Western Blot method is negative. These transitory false-positive results may due to IgM production in response to the vaccine.

4.6 Pregnancy and lactation

There are currently no data available on the use of Focetria in pregnancy. Data from pregnant women vaccinated with different inactivated non-adjuvanted seasonal vaccines do not suggest malformations or fetal or neonatal toxicity.

An animal study with H5N1 mock-up vaccine did not indicate reproductive toxicity (see section 5.3).

The use of Focetria may be considered during pregnancy if this is thought to be necessary, taking into account official recommendations.

Focetria may be used in lactating women.

4.7 Effects on ability to drive and use machines

Some of the effects mentioned under section 4.8 “Undesirable Effects” may affect the ability to drive or use machines.

4.8 Undesirable effects

- Clinical trials

Adverse reactions reported are listed according to the following frequency:

Very common ($\geq 1/10$),

Common ($\geq 1/100$ to $< 1/10$),

Uncommon ($\geq 1/1,000$ to $< 1/100$),

Rare ($\geq 1/10,000$ to $< 1/1,000$),

Very rare ($< 1/10,000$).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:

Adults and elderly

In an ongoing clinical trial 131 adults and 123 elderly were exposed to two doses of the 7.5 μg Focetria (H1N1) pandemic vaccine. The safety profile of Focetria was similar to that of the H5N1 mock up vaccines. Most of the reactions were mild in nature and of short duration. The incidence of symptoms observed in subjects over 60 years of age was generally lower as compared to the 18-60 years old population.

Very common: pain, induration and erythema, myalgia, headache, sweating, malaise and fatigue

In clinical trials with different formulations (H5N3, H9N2 and H5N1) approximately 3400 subjects were exposed to the candidate vaccine.

Most of the reactions were mild in nature, of short duration and qualitatively similar to those induced by conventional seasonal influenza vaccines. It is widely accepted that the adjuvant effect leading to increased immunogenicity is associated with a slightly higher frequency of local reactions (mostly mild pain) compared with conventional, nonadjuvanted influenza vaccines. There were fewer reactions after the second vaccination compared with the first.

Adverse reactions from clinical trials with the mock-up vaccine are listed below (see section 5.1 for more information on mock-up vaccines and Focetria).

The incidence of symptoms observed in subjects over 60 years of age was lower as compared to the 18-60 years old population.

Nervous system disorders

Very common: headache

Rare: convulsions

Skin and subcutaneous tissue disorders

Common: sweating

Uncommon: urticaria

Rare: eye swelling

Musculoskeletal, connective tissue and bone disorders

Very common: myalgia

Common: arthralgia

Gastrointestinal disorders

Common: nausea

General disorders and administration site conditions

Very common: injection site swelling, injection site pain, injection site induration, injection site redness, fatigue, malaise and shivering

Common: injection site ecchymosis and fever

Uncommon: influenza like illness

Rare: anaphylaxis

The common reactions usually disappear within 1-2 days without treatment.

Children and adolescents 6 months to 17 years of age

Clinical trials with Focetria (H1N1)

Safety data after the first and second dose in children and adolescents suggest a comparable safety profile with that reported for the H5N1 mock-up vaccine formulation.

Adverse reactions in the week following vaccination from 87 children 3-8 years old and 95 children and adolescents 9-17 years old, receiving the 7.5 µg formulation were reported as follows:

	Injection 1	Injection 2
Children (3 to 8 years of age)	N=87	N=85
Any adverse reaction	67%	61%
Local	56%	49%
Systemic	32%	31%
Fever $\geq 38^{\circ}\text{C}/\geq 39^{\circ}\text{C}/\geq 40^{\circ}\text{C}$	3% / 0% / 0%	1% / 1% / 0%
Any other AE	13%	15%
Adolescents (9 to 17 years of age)	N=95	N=94
Any adverse reaction	67%	55%
Local	60%	49%
Systemic	38%	26%
Fever $\geq 38^{\circ}\text{C}/\geq 39^{\circ}\text{C}/\geq 40^{\circ}\text{C}$	2% / 0% / 0%	1% / 0% / 0%
Any other AE	11%	9%

Data in children and adolescents 3-17 years suggest a slight decrease in reactogenicity after the second dose, with no increase in rates of fever.

Very common reactions reported in children and adolescents 3 to 17 years of age:

Pain, induration and erythema, malaise, myalgia, headache and fatigue.

Data from 81 children 12-35 months old receiving the 7.5 µg formulation, 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:

Tenderness, induration and erythema, irritability, unusual crying, sleepiness, diarrhoea and change in eating habits.

Fever ($\geq 38^{\circ}\text{C}$) has been reported by 14% of subjects 12-35 months old with one subject (1%) reporting fever $\geq 40^{\circ}\text{C}$.

Clinical trials with the H5N1 Mock-up vaccine

A clinical trial was conducted with a H5N1 vaccine combined with MF59C.1 adjuvant in 471 children from 6 months to 17 years of age. Two doses of vaccine containing H5N1 (A/Vietnam/1194/2004) at the dosage of 7.5 µg hemagglutinin [HA]/dose with MF59C.1 adjuvant were administered three weeks apart. The effect of the administration of a booster dose 12 months following the second dose has also been evaluated.

Local and systemic reactogenicity was monitored for the week following vaccine administration. Local reactions were more frequent at subsequent administrations following the first one, at any age.

Most systemic reactions were experienced within 3 days following vaccination and were transient and mild of moderate severity.

In these age groups, the per-dose frequency of reactions was higher than the one reported for adults and elderly. A higher frequency of fever >39.0°C was also observed.

Systemic adverse events reported very commonly in the 6 months-35 months of age group per dose were irritability, unusual crying, sleepiness, diarrhoea and change in eating habits. In children very common systemic events included headache, fatigue. Among the adolescents the very common events were: malaise, myalgia, headache, fatigue, sweating, nausea, chills.

Percentages of subjects with solicited and unsolicited reactions are provided below:

	Injection 1	Injection 2
Toddlers (6-35 months months)	N=145	N=138
Local	47%	46%
Systemic	59%	51%
Fever $\geq 38^{\circ}\text{C}/\geq 39^{\circ}\text{C}/\geq 40^{\circ}\text{C}$	7% / 1% / 0%	12% / 3% / 0%
Any other AE	54%	49%
Children (3 – 8 years of age)	N=96	N=93
Local	66%	58%
Systemic	32%	33%
Fever $\geq 38^{\circ}\text{C}/\geq 39^{\circ}\text{C}/\geq 40^{\circ}\text{C}$	4% / 1% / 0%	2% / 0% / 0%
Any other AE	36%	31%
Adolescents (9 -17 years of age)	N=93	N=91
Local	81%	70%
Systemic	69%	52%
Fever $\geq 38^{\circ}\text{C}/\geq 39^{\circ}\text{C}/\geq 40^{\circ}\text{C}$	0% / 0% / 0%	1% / 0% / 0%
Any other AE	30%	27%

- Post-marketing surveillance

Focetria (H1N1)

In addition to the adverse reactions reported in the clinical trials, the following have been reported during post-marketing experience with Focetria H1N1:

Blood and lymphatic system disorders

Lymphadenopathy.

Cardiac disorders

Palpitation, tachycardia.

General disorders and administration site conditions

Asthenia.

Musculoskeletal, connective tissue and bone disorders

Muscular weakness, pain in extremities.

Respiratory disorders

Cough.

Skin and subcutaneous tissue disorders

Generalised skin reactions including pruritus, urticaria or non-specific rash; angioedema.

Gastrointestinal disorders

Gastrointestinal disorders such as nausea, vomiting, abdominal pain and diarrhoea.

Nervous system disorders

Headache, dizziness, somnolence, syncope. Neurological disorders, such as neuralgia, paraesthesia, convulsions and neuritis.

Immune system disorders

Allergic reactions, anaphylaxis including dyspnoea, bronchospasm, laryngeal oedema, in rare cases leading to shock.

In addition, from Post-marketing surveillance with seasonal trivalent vaccines in all age groups and with the MF59 adjuvanted seasonal trivalent vaccine with the similar composition of Focetria (surface antigen, inactivated, adjuvanted with MF59C.1), licensed for use in elderly subjects above 65 years of age, the following adverse events have been reported:

Rare:

Transient thrombocytopenia.

Very rare:

Vasculitis with transient renal involvement and exudative erythema multiforme.
Neurological disorders, such as encephalomyelitis and Guillain Barré syndrome.

Thiomersal:

This medicinal product contains thiomersal (an organomercuric compound) as a preservative and therefore, it is possible that sensitisation reactions may occur (see section 4.4).

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccine, ATC Code: J07BB02

This medicinal product has been authorised under “Exceptional Circumstances”.

The European Medicines Agency (EMA) will regularly review any new information which may become available and this SPC will be updated as necessary.

Mock-up vaccines contain influenza antigens that are different from those in the currently circulating influenza viruses. These antigens can be considered as ‘novel’ antigens and simulate a situation where the target population for vaccination is immunologically naïve.

Data obtained with a mock-up vaccine will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical immunogenicity, safety and reactogenicity data obtained with mock-up vaccines are relevant for the pandemic vaccines.

Clinical studies with Focetria (H1N1) currently provide:

- Available safety and immunogenicity data obtained after administration of a one or two doses of Focetria (H1N1) to healthy children and adolescents aged 3-17 years and to healthy adults, including the elderly.

Clinical studies in which a version of Focetria containing HA derived from A/Vietnam/1194/2004 (H5N1) was administered at day 1 and at day 22 provide:

- Safety and immunogenicity data in healthy children and adolescents aged from 6 months to 17 years and in adults, including the elderly

Immune response to Focetria (H1N1)

- Studies in adults and elderly

Immunogenicity results with two doses of 7.5 µg Focetria (H1N1) pandemic vaccine from the ongoing clinical trial in adults and elderly are shown below.

The seroprotection rate*, seroconversion rate* and the seroconversion factor ** for anti-HA antibody to A/H1N1 in adult and elderly subjects by HI assay after administration of 7.5 µg of Focetria were as follows:

Anti-HA antibody	Adults (18-60 years)			
	21 days after 1 st dose(day 22)		21 days after 2 nd 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

Anti-HA antibody	Elderly (>60 years)			
	21 days after 1 st dose(day 22)		21 days after 2 nd 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)

- Studies in children

The seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibody to H1N1 in children and adolescents aged 9-17 years by HI assay administration of 7.5 µg of Focetria were as follows:

Anti-HA antibody	Children and Adolescents (9-17 years)			
	21 days after 1 st dose(day 22)		21 days after 2 nd 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.

Data on responses to a second dose administered after an interval of three weeks showed an increase in overall GMT from 793 to 1065 (N=88) and an increase in GMT from 522 to 870 in children who were seronegative at baseline (N=51).

The seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibody to H1N1 in children aged 3-8 years by HI assay after administration of 7.5 µg of Focetria were as follows:

Anti-HA antibody	Children (3-8 years)			
	21 days after 1 st dose(day 22)		21 days after 2 nd 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)

Data on responses to a second dose administered after an interval of three weeks showed an increase in overall GMT from 319 to 702 (N=70) and an increase in GMT from 247 to 726 in children who were seronegative at baseline (N=48).

The seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibody to H1N1 in children aged 12-35 months by HI assay after a single dose of 7.5 µg of Focetria were as follows:

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)

Limited data available on responses to a second dose administered after an interval of three weeks showed an increase in overall GMT from 333 to 976 (N=871) and an increase in GMT from 237 to 776 in children who were seronegative at baseline (N=46).

Immune response to mock-up H5N1 vaccine:

- **Studies in adults and elderly**

A clinical trial was conducted with a H5N1 vaccine combined with MF59C.1 adjuvant in 486 healthy adult volunteers. Two doses of vaccine containing H5N1 (A/Vietnam/1194/2004) (7.5 µg hemagglutinin [HA]/dose) with MF59C.1 adjuvant were administered three weeks apart.

The seroprotection rate* seroconversion rate* and the seroconversion factor ** for anti-HA antibody to H5N1 A/Vietnam/1194/2004 in the adults measured by SRH were as follows:

Anti-HA antibody	21 days after 1 st dose	21 days after 2 nd dose
Seroprotection rate	41% (95% CI: 33-49)	86% (95% CI: 79-91)
Seroconversion rate	39% (95% CI: 31-47)	85% (95% CI: 79-91)
Seroconversion factor	2.42 (2.02-2.89)	7.85 (6.7-9.2)

* measured by SRH assay $\geq 25 \text{ mm}^2$

** geometric mean ratios of SRH

The seroprotection rate* seroconversion rate* and the seroconversion factor ** for anti-HA antibody to H5N1 A/Vietnam/1194/2004 in subjects aged over 60 measured by SRH were as follows:

Anti-HA antibody	21 days after 1 st dose	21 days after 2 nd dose
Seroprotection rate	53% (95% CI: 42-64)	81% (95% CI: 71-89)
Seroconversion rate	45% (95% CI: 34-56)	71% (95% CI: 60-81)
Seroconversion factor	2.85 (2.22-3.66)	5.02 (3.91-6.45)

* measured by SRH assay $\geq 25 \text{ mm}^2$

** geometric mean ratios of SRH

Limited data on the persistence of antibodies in elderly immunised with the H5N1 mock-up vaccine showed that up to 50% of the subjects were seroprotected at six months.

Cross-reactivity of highly pathogenic variants of A/Vietnam/1194/2004 (H5N1) in subjects 18 years and above.

Immunogenicity analyses were carried out for influenza A/H5N1/turkey/Turkey/05 (NIBRG23; clade 2.2) with HI, SRH, and MN and for influenza A/H5N1/Indonesia (clade 2.1) with HI and MN, on sera collected 3 weeks after the second vaccination (day 43) and 3 weeks after the booster vaccination (day 223).

In both age groups the responses to the heterologous strains highly increased after booster vaccination with the mock-up vaccine by all assays used.

- **Studies in children**

A clinical trial was conducted with a H5N1 vaccine combined with MF59C.1 adjuvant in 471 children from 6 months to 17 years of age. Two doses of vaccine containing H5N1 (A/Vietnam/1194/2004) at the dosage of 7.5 µg hemagglutinin [HA]/dose with MF59C.1 adjuvant were administered three weeks apart.

The seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibody to H5N1 A/Vietnam/1194/2004 in the toddlers aged from 6 to 35 months measured by SRH were as follows:

Anti-HA antibody	21 days after 1 st dose	21 days after 2 nd dose
Seroprotection rate	47% (CI: 38-55)	100% (CI: 97-100)
Seroconversion rate	44% (CI: 36-53)	98% (CI: 95-100)
Seroconversion factor	2.67 (2.24-3.18)	16 (14-18)

* measured by SRH assay $\geq 25 \text{ mm}^2$

** geometric mean ratios of SRH

The seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibody to H5N1 A/Vietnam/1194/2004 in the children aged from 3 to 8 years measured by SRH were as follows:

Anti-HA antibody	21 days after 1 st dose	21 days after 2 nd dose
Seroprotection rate	54% (CI: 44-65)	100% (CI: 96-100)
Seroconversion rate	56% (CI: 45-66)	100% (CI: 96-100)
Seroconversion factor	3.34 (2.74-4.06)	15 (13-17)

* measured by SRH assay $\geq 25 \text{ mm}^2$

** geometric mean ratios of SRH

The seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibody to H5N1 A/Vietnam/1194/2004 in the adolescent aged from 9 to 17 years measured by SRH were as follows:

Anti-HA antibody	21 days after 1 st dose	21 days after 2 nd dose
Seroprotection rate	59% (CI: 48-69)	100% (CI: 96-100)
Seroconversion rate	57% (CI: 46-67)	99% (CI: 94-100)
Seroconversion factor	3.87 (3.25-4.61)	14 (12-16)

* measured by SRH assay $\geq 25 \text{ mm}^2$

** geometric mean ratios of SRH

- Supportive Studies

In two dose finding studies 78 adults received an adjuvanted mock-up vaccine (H5N3 or H9N2). Two doses of vaccine with H5N3 (A/Duck/Singapore/97) strain at 3 different dosages (7.5, 15 and 30 μg HA/dose) were administered three weeks apart.

Serum samples were tested against the original H5N3 and also a number of H5N1 isolates.

Serologic responses obtained with the SRH assay showed that 100% of subjects achieved seroprotection and 100% seroconverted after two 7.5 μg injections. The adjuvanted vaccine was also found to induce antibodies that cross-protected against the H5N1 strains isolated in 2003 and 2004, which exhibit some antigenic drift compared to the original strains.

Two doses of vaccine containing H9N2 (A/chicken/Hong Kong/G9/97) strain at 4 different dosages (3.75, 7.5, 15 and 30 μg HA/dose), were administered four weeks apart. Serologic responses obtained with the Hemagglutination Inhibition (HI) assay showed that 92% of subjects achieved seroprotection and 75% seroconverted after two 7.5 μg injections.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data obtained with the mock-up vaccine (MF59C.1-adjuvanted H5N1 vaccine) and with seasonal vaccine containing MF59C.1 adjuvant reveal no special hazard for humans based on conventional studies of efficacy, repeated dose toxicity, and reproductive and developmental toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride,
Potassium chloride,
Potassium dihydrogen phosphate,
Disodium phosphate dihydrate,
Magnesium chloride hexahydrate,
Calcium chloride dihydrate,
Sodium citrate,
Citric acid,
Thiomersal,
Water for injections.

For the adjuvant, see section 2.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

1 year.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze. Store in the original package in order to protect from light.

6.5 Nature and contents of container

5.0 ml in 10-dose vial (type I glass) with stopper (halo-butyl rubber). Packs of 10.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Gently shake the multidose vial each time before withdrawing a dose (0.5 ml) of the vaccine into a syringe. Prior to administration, the withdrawn vaccine should be allowed reach room temperature.

Although Focetria in multidose vials contains a preservative that inhibits microbial growth, minimisation of the risk of contamination of the multidose vial during withdrawal of each dose is the responsibility of the user.

Record date and time of the first dose withdrawal on the vial label.

Between uses, return the multidose vial to the recommended storage conditions between 2° and 8° C (36° and 46° F). The multidose vial should preferably be used within 24 hours after first withdrawal.

Preliminary data are also available that suggest that multidose vials could be used up to a maximum of 72 hours after first withdrawal, although such pro-longed storage periods should not be the preferred option.

Any unused vaccine or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Vaccines and Diagnostics S.r.l. - Via Fiorentina, 1 – Siena, Italy.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/385/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 May 2007

10. DATE OF REVISION OF THE TEXT

02/2010

Detailed information on this product is available on the website of the European Medicines Agency (EMA):
<http://www.ema.europa.eu/>.