

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

* 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

This pandemic influenza vaccine H1N1 has been authorised based on data obtained with a version containing H5N1 antigen supplemented with data obtained with the vaccine containing H1N1 antigen.
The Clinical Particulars section will be updated in accordance with emerging additional data.

There is currently limited clinical experience with Focetria (H1N1) in healthy adults, including the elderly (see section 5.1) and no clinical experience in children or in adolescents. The decision to use Focetria (H1N1) in each age group defined below should take into account the extent of the clinical data available with a version of the vaccine containing H5N1 antigen and the disease characteristics of the current influenza pandemic.

The dose recommendations are based on the:

- safety and immunogenicity data available on the administration of the MF59C.1 adjuvanted vaccine containing 7.5 µg HA derived from A/Vietnam/1194/2004 (H5N1) at 0 and 21 days to adults, including the elderly, and children between 6 months and 17 years of age.
- currently available immunogenicity data obtained three weeks after administration of a single dose of Focetria (H1N1) to a limited number of healthy adults, including the elderly.

See sections 4.8 and 5.1.

Posology:

Adults (18-60 years):

One dose of 0.5 ml at an elected date.

A second dose of vaccine should preferably be given. There should be an interval of at least three weeks between the first and second dose.

However, the currently available immunogenicity data obtained at three weeks after administration of Focetria (H1N1) to a limited number of healthy adults aged 18-60 years suggest that a single dose may be sufficient in this age group.

See section 5.1.

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.

A second dose of vaccine should preferably be given. There should be an interval of at least three weeks between the first and second dose.

However in selecting the dosing regimen, consideration may also be given to the currently available immunogenicity data obtained at three weeks after administration of Focetria (H1N1) to a limited number of healthy adults.

See sections 4.8 and 5.1.

Children and adolescents 6 months to 8 years of age:

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, complete the vaccination course with Focetria (see section 4.4).

For further information, see sections 4.8 and 5.1.

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 or subcutaneously.

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

Data on co-administration of subunit non-adjuvanted influenza seasonal and H5N1 vaccines in adults do not suggest any interference in the immune response to seasonal or to H5N1 antigens. There were no differences in serious adverse events (SAEs) between groups, and all SAEs were unrelated. These data suggest that Focetria can be given at the same time as non-adjuvanted subunit seasonal influenza vaccines.

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

However, 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.

The immunological response may be diminished if the patient is undergoing immunosuppressant treatment.

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 134 adults and 123 elderly were exposed to one dose 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 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

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 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

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:

Uncommon:

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

Rare:

Neuralgia, paraesthesia, convulsions, transient thrombocytopenia.

Allergic reactions, in rare cases leading to shock, have been reported.

Very rare:

Vasculitis with transient renal involvement and exudative erythema multiforme.

Neurological disorders, such as encephalomyelitis, neuritis 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.

This section describes the clinical experience with the mock-up vaccines following a two-dose administration and with Focetria (H1N1) after a single dose in healthy adults, including the elderly. 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.

Immunogenicity results with a single dose 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 were as follows:

Anti-HA antibody	Adults (18-60 years)		Elderly (>60 years)	
	Total N=132	Seronegative at baseline N = 50	Total N=122	Seronegative at baseline N = 27
Seroprotection rate (Day 22)	96% (95%CI: 91-99)	98 % (95%CI: 89-100)	72% (95%CI: 63-80)	56% (95%CI: 35-75)
GMR (Day 22 to Day 1)	18 (95%CI: 13-24)	65 (95%CI: 41-103)	4 (95%CI:3.12 -5.13)	9.58 (95%CI: 5.86-16)
Seroconversion or Significant Increase (Day 22)	88% (95%CI: 81-93)	98% (95%CI: 89-100)	43% (95%CI:34-52)	56% (95%CI: 35-75)

* measured by HI assay

** geometric mean ratios of HI

In the elderly, the proportion of seronegative subjects who were seroprotected following one dose of Focetria was 56%, while 77% of seropositive subjects showed seroprotection. The seroconversion rate in the seropositive subjects was 39%.

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

10/2009

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

This pandemic influenza vaccine H1N1 has been authorised based on data obtained with a version containing H5N1 antigen supplemented with data obtained with the vaccine containing H1N1 antigen.
The Clinical Particulars section will be updated in accordance with emerging additional data.

There is currently limited clinical experience with Focetria (H1N1) in healthy adults, including the elderly (see section 5.1) and no clinical experience in children or in adolescents.

The decision to use Focetria (H1N1) in each age group defined below should take into account the extent of the clinical data available with a version of the vaccine containing H5N1 antigen and the disease characteristics of the current influenza pandemic.

The dose recommendations are based on the:

- safety and immunogenicity data available on the administration of the MF59C.1 adjuvanted vaccine containing 7.5 µg HA derived from A/Vietnam/1194/2004 (H5N1) at 0 and 21 days to adults, including the elderly, and children between 6 months and 17 years of age.
- currently available immunogenicity data obtained three weeks after administration of a single dose of Focetria (H1N1) to a limited number of healthy adults, including the elderly.

See sections 4.8 and 5.1.

Posology:

Adults (18-60 years):

One dose of 0.5 ml at an elected date.

A second dose of vaccine should preferably be given. There should be an interval of at least three weeks between the first and second dose.

However, the currently available immunogenicity data obtained at three weeks after administration of Focetria (H1N1) to a limited number of healthy adults aged 18-60 years suggest that a single dose may be sufficient in this age group.

See section 5.1.

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.

A second dose of vaccine should preferably be given. There should be an interval of at least three weeks between the first and second dose.

However in selecting the dosing regimen, consideration may also be given to the currently available immunogenicity data obtained at three weeks after administration of Focetria (H1N1) to a limited number of healthy adults.

See sections 4.8 and 5.1.

Children and adolescents 6 months to 8 years of age:

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, complete the vaccination course with Focetria (see section 4.4).

For further information, see sections 4.8 and 5.1.

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 or subcutaneously.

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

Data on co-administration of subunit influenza non-adjuvanted seasonal and H5N1 vaccines in adults do not suggest any interference in the immune response to seasonal or to H5N1 antigens. There were no differences in serious adverse events (SAEs) between groups, and all SAEs were unrelated. This data suggest that Focetria can be given at the same time as non-adjuvanted subunit seasonal influenza vaccines. There are no data on co-administration of Focetria with other vaccines.

However, 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. The immunological response may be diminished if the patient is undergoing immunosuppressant treatment.

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

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Very common:

pain, induration and erythema, myalgia, headache, sweating 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

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, diarrhea 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

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:

Uncommon:

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

Rare:

Neuralgia, paraesthesia, convulsions, transient thrombocytopenia.
Allergic reactions, in rare cases leading to shock, have been reported.

Very rare:

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

This section describes the clinical experience with the mock-up vaccines following a two-dose administration and with Focetria (H1N1) after a single dose in healthy adults, including the elderly. 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.

Immunogenicity results with a single dose 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 were as follows:

Anti-HA antibody	Adults (18-60 years)		Elderly (>60 years)	
	Total N=132	Seronegative at baseline N = 50	Total N=122	Seronegative at baseline N = 27
Seroprotection rate	96% (95%CI: 91-99)	98 % (95%CI: 89-	72% (95%CI: 63-80)	56% (95%CI: 35-75)

(Day 22)		100)		
GMR (Day 22 to Day 1)	18 (95%CI: 13-24)	65 (95%CI: 41-103)	4 (95%CI:3.12 -5.13)	9.58 (95%CI: 5.86-16)
Seroconversion or Significant Increase (Day 22)	88% (95%CI: 81-93)	98% (95%CI: 89-100)	43% (95%CI:34-52)	56% (95%CI: 35-75)

* measured by HI assay

** geometric mean ratios of HI

In the elderly, the proportion of seronegative subjects who were seroprotected following one dose of Focetria was 56%, while 77% of seropositive subjects showed seroprotection. The seroconversion rate in the seropositive subjects was 39%.

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.

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

10/2009

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