Product Information as approved by the CHMP on 22 April 2010, pending endorsement by the European Commission

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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Focetria suspension for injection in pre-filled syringe
~~Pandemic~~ Influenza vaccine **(H1N1)v** (surface antigen, inactivated, adjuvanted)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

A/California/**0**7/2009 (H1N1)~~v like~~ **- derived** strain **used NYMC** ~~(~~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 recommendation 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 **caused by A(H1N1) 2009 virus.** ~~in an officially declared pandemic situation~~ (See section~~s~~ 4.**4** ~~4.2 and 5.1~~).
~~Pandemic~~ Influenza vaccine should be used in accordance with Official Guidance.

4.2 Posology and method of admnistration

The dose recommendations take into account **the safety and immunogenicity** 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 **are available in** ~~(~~children aged less than 6 months~~) with one or both versions of Focetria as detailed in~~ **(see** 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 **one dose** ~~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 **3** ~~9~~-17 years:
One dose of 0.5 ml at an elected date.
Immunogenicity data obtained at three weeks after **one dose** ~~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.

~~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.
There is a further immune response to a second dose of 0.5 ml administered after an interval of three weeks.
~~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 **H1N1** (see section 4.4).
The use of a second dose should take into consideration the information provided in sections 4.4, 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

The vaccine can only be expected to protect against influenza caused by A/California/07/2009 (H1N1)v-like strains.

Caution is needed when administrating 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 shall 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**)v** ~~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

It is estimated that more than 90,000 women have been vaccinated during pregnancy with Focetria (H1N1).~~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.~~

However information on the number of outcomes is currently limited. Preliminary data on outcomes from spontaneously reported events and ongoing post-marketing studies (pregnancy registry and

prospective interventional study) do not suggest direct or indirect harmful effects with respect to pregnancy.
Data from pregnant women vaccinated with different inactivated non-adjuvanted seasonal vaccines do not suggest malformations or foetal or neonatal toxicity.

~~Healthcare providers need to assess the benefit and potential risks of administering the vaccine to pregnant women taking into account official recommendations.~~

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 **has to** ~~if this is thought to be necessary,~~ tak~~eing~~ into account official recommendations.

Focetria may be **administered to** ~~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 (≥1/10),
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100),
Rare (≥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 a~~n 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

Muscoskeletal, 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 ≥38°C to 38.9°C ~~/ Fever 39°C to 39.9°C / ≥ Fever <40°C/~~	3% ~~/ 0% / 0%~~	1% ~~/ 1% / 0%~~
Fever 39°C to 39.9°C	**0%**	**1%**
Fever ≥ 40° C	**0%**	**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 ≥38°C to 38.9°C ~~/ Fever 39°C to 39.9°C / ≥ Fever <40°C/~~	2% ~~/ 0% / 0%~~	1% ~~/ 0% / 0%~~
Fever 39°C to 39.9°C	**0%**	**0%**
Fever ≥ 40° C	**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.

Adverse reactions in the week following vaccination from 80 infants 6-11 months old and 82 toddlers 12-35 months old, receiving the 7.5 µg formulation were reported as follows:

	Injection 1	**Injection 2**
Infants (6 to 11 months of age)	**N=80**	**N=75**
Any adverse reaction	**79%**	**65%**
Local	**44%**	**29%**
Systemic	**69%**	**55%**
Fever ≥38°C to 38.9°C	**9%**	**6%**
Fever 39°C to 39.9°C	**2%**	**4%**
Fever ≥ 40° C	**0%**	**0%**
Any other AE	**29%**	**28%**
Toddlers (12 to 35 months of age)	**N=82**	**N=81**
Any adverse reaction	**70%**	**70%**
Local	**50%**	**48%**
Systemic	**55%**	**44%**
Fever ≥38°C to 38.9°C	**10%**	**11%**
Fever 39°C to 39.9°C	**4%**	**1%**
Fever ≥ 40° C	**1%**	**0%**
Any other AE	**21%**	**22%**

Data in infants and toddlers 6-35 months of age suggest a slight decrease in reactogenicity after the second dose, with no increase in rates of fever.

~~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 **233 infants and toddlers** ~~children 12~~ **6** to 35 months of age:
Tenderness, ~~induration and~~ erythema, irritability, unusual crying, sleepiness, diarrhoea and change in eating habits. **Induration was a common reaction in toddlers but was less common in infants.**

~~Fever (≥38°C) has been reported by 14% of subjects 12-35 months old with one subject (1%) reporting fever ≥40°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 to 35 months)**~~	~~**N=145**~~	~~**N=138**~~
~~Local~~	~~47%~~	~~46%~~
~~Systemic~~	~~59%~~	~~51%~~
~~Fever ≥ 38°C/≥ 39°C/≥ 40° 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 ≥ 38°C/≥ 39°C/≥ 40° 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 ≥ 38°C/≥ 39°C/≥ 40°C~~	~~0% / 0% / 0%~~	~~1% / 0% / 0%~~
~~Any other AE~~	~~30%~~	~~27%~~

- Post-marketing surveillance

Focetria (H1N1)**v**

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

Blood and lymphatic system disorders
Lymphadenopathy.

Cardiac disorders
Palpitation, tachycardia.

General disorders and administration site conditions
Asthenia.

Muscoskeletal, 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~~ **6 months** -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:

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

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

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

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

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

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:

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

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

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~~ **administration** of 7.5 µg of Focetria were as follows:

Children 12-35 months				
Anti-HA antibody	**21 days after 1st dose(day 22)**		**21 days after 2nd dose (day 43)**	
	Total N=66	**Seronegative at baseline N=45**	**Total N=66**	**Seronegative at baseline N=45**
Seroprotection rate (95% CI)	**100% (95-100)**	**100% (92-100)**	**100% (95-100)**	**100% (92-100)**
GMR (95% CI)	**33 (21-51)**	**48 (29-79)**	**93 (54-159)**	**145 (88-238)**
Seroconversion or Significant Increase (95% CI)	**100% (95-100)**	**100% (92-100)**	**100% (95-100)**	**100% (92-100)**

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)

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

~~Limited~~ Data ~~available~~ on responses to a second dose administered after an interval of three weeks showed an increase in overall GMT from ~~333~~ **307** to ~~976~~ **873** (N=~~871~~**66**) and an increase in GMT from ~~237~~ **243** to ~~776~~ **733** in children who were seronegative at baseline (N=~~46~~**45**).

The seroprotection rate*, seroconversion rate* and the seroconversion factor for anti-HA antibody to H1N1 in infants aged 6-11 months by HI assay after administration of 7.5 µg of Focetria were as follows:**

Infants 6-11 months				
Anti-HA antibody	**21 days after 1st dose(day 22)**		**21 days after 2nd dose (day 43)**	
	Total N=57	**Seronegative at baseline N=37**	**Total N=57**	**Seronegative at baseline N=37**
Seroprotection rate (95% CI)	**100% (94-100)**	**100% (91-100)**	**100% (94-100)**	**100% (91-100)**
GMR (95% CI)	**21 (14-30)**	**32 (18-55)**	**128 (74-221)**	**274 (196-383)**
Seroconversion or Significant Increase (95% CI)	**96% (88-100)**	**100% (91-100)**	**98% (91-100)**	**100% (91-100)**

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

Data on responses to a second dose administered after an interval of three weeks showed an increase in overall GMT from 274 to 1700 (N=57) and an increase in GMT from 162 to 1399 in children who were seronegative at baseline (N=37).

~~**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 1st dose~~	~~21 days after 2nd 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 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 1st dose	21 days after 2nd 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 ≥ 25 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 1st dose	21 days after 2nd 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 ≥ 25 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 1st dose	21 days after 2nd 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 ≥ 25 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 1st dose	21 days after 2nd 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 ≥ 25 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.~~

Additional information is available from the studies conducted with a vaccine similar in composition to Focetria but containing antigen derived from H5N1 viruses. Please consult the Product Information of Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted).

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

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 **(H1N1)v** (surface antigen, inactivated, adjuvanted)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

A/California/**0**7/2009 (H1N1)~~v like~~ **- derived** strain **used NYMC** ~~(~~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

~~This vaccine complies with the WHO recommendation 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 **caused by A(H1N1) 2009 virus.** ~~in an officially declared pandemic situation~~ (See section~~s~~ 4.**4** ~~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 **the safety and immunogenicity** 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 **are available in** ~~(~~children aged less than 6 months~~)~~ ~~with one or both versions of Focetria as detailed in~~ **(see** 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 **one dose** ~~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 **3** ~~9~>-17 years:
One dose of 0.5 ml at an elected date.
Immunogenicity data obtained at three weeks after **one dose** ~~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.

~~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.
There is a further immune response to a second dose of 0.5 ml administered after an interval of three weeks.
~~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 **H1N1** (see section 4.4).
The use of a second dose should take into consideration the information provided in sections 4.4, 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

The vaccine can only be expected to protect against influenza caused by A/California/07/2009 (H1N1)v-like strains.

Caution is needed when administrating 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 shall 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**)v** ~~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

It is estimated that more than 90,000 women have been vaccinated during pregnancy with Focetria (H1N1).~~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.~~

However information on the number of outcomes is currently limited. Preliminary data on outcomes from spontaneously reported events and ongoing post-marketing studies (pregnancy registry and prospective interventional study) do not suggest direct or indirect harmful effects with respect to pregnancy.
Data from pregnant women vaccinated with different inactivated non-adjuvanted seasonal vaccines do not suggest malformations or foetal or neonatal toxicity.

~~Healthcare providers need to assess the benefit and potential risks of administering the vaccine to pregnant women taking into account official recommendations.~~

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 **has to** ~~if this is thought to be necessary,~~ tak~~eing~~ into account official recommendations.

Focetria may be **administered to** ~~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 (≥1/10),
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100),
Rare (≥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 a~~n 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

Muscoskeletal, 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 ≥38°C to 38.9°C ~~/ Fever 39°C to 39.9°C / ≥ Fever <40°C/~~	3% ~~/ 0% / 0%~~	1% ~~/ 1% / 0%~~
Fever 39°C to 39.9°C	**0%**	**1%**
Fever ≥ 40° C	**0%**	**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 ≥38°C to 38.9°C ~~/ Fever 39°C to 39.9°C / ≥ Fever <40°C/~~	2% ~~/ 0% / 0%~~	1% ~~/ 0% / 0%~~
Fever 39°C to 39.9°C	**0%**	**0%**

Fever ≥ 40° C	**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.

Adverse reactions in the week following vaccination from 80 infants 6-11 months old and 82 toddlers 12-35 months old, receiving the 7.5 µg formulation were reported as follows:

	Injection 1	**Injection 2**
Infants (6 to 11 months of age)	**N=80**	**N=75**
Any adverse reaction	**79%**	**65%**
Local	**44%**	**29%**
Systemic	**69%**	**55%**
Fever ≥38°C to 38.9°C	**9%**	**6%**
Fever 39°C to 39.9°C	**2%**	**4%**
Fever ≥ 40° C	**0%**	**0%**
Any other AE	**29%**	**28%**
Toddlers (12 to 35 months of age)	**N=82**	**N=81**
Any adverse reaction	**70%**	**70%**
Local	**50%**	**48%**
Systemic	**55%**	**44%**
Fever ≥38°C to 38.9°C	**10%**	**11%**
Fever 39°C to 39.9°C	**4%**	**1%**
Fever ≥ 40° C	**1%**	**0%**
Any other AE	**21%**	**22%**

Data in infants and toddlers 6-35 months of age suggest a slight decrease in reactogenicity after the second dose, with no increase in rates of fever.

~~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 **233 infants and toddlers** ~~children 12~~ **6** to 35 months of age:
Tenderness, ~~induration and~~ erythema, irritability, unusual crying, sleepiness, diarrhoea and change in eating habits. **Induration was a common reaction in toddlers but was less common in infants.**

~~Fever (≥38°C) has been reported by 14% of subjects 12-35 months old with one subject (1%) reporting fever ≥40°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 to 35 months)**~~	~~**N=145**~~	~~**N=138**~~
~~Local~~	~~47%~~	~~46%~~
~~Systemic~~	~~59%~~	~~51%~~
~~Fever ≥ 38°C/≥ 39°C/≥ 40° 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 ≥ 38°C/≥ 39°C/≥ 40° 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 ≥ 38°C/≥ 39°C/≥ 40°C~~	~~0% / 0% / 0%~~	~~1% / 0% / 0%~~
~~Any other AE~~	~~30%~~	~~27%~~

- Post-marketing surveillance

Focetria (H1N1)**v**

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

Blood and lymphatic system disorders
Lymphadenopathy.

Cardiac disorders
Palpitation, tachycardia.

General disorders and administration site conditions
Asthenia.

Muscoskeletal, 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 one or two doses of Focetria (H1N1) to healthy children and adolescents aged ~~3~~ **6 months** -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:

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

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

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

- 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 1st dose(day 22)		21 days after 2nd dose (day 43)	
	Total	Seronegative at	Total	Seronegative at

	N=88	baseline N=51	N=88	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:

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

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

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~~ **administration** of 7.5 µg of Focetria were as follows:

Children 12-35 months				
Anti-HA antibody	**21 days after 1st dose(day 22)**		**21 days after 2nd dose (day 43)**	
	Total N=66	**Seronegative at baseline N=45**	**Total N=66**	**Seronegative at baseline N=45**
Seroprotection rate (95% CI)	**100% (95-100)**	**100% (92-100)**	**100% (95-100)**	**100% (92-100)**
GMR (95% CI)	**33 (21-51)**	**48 (29-79)**	**93 (54-159)**	**145 (88-238)**

Seroconversion or Significant Increase (95% CI)	**100% (95-100)**	**100% (92-100)**	**100% (95-100)**	**100% (92-100)**

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)

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

~~Limited~~ Data ~~available~~ on responses to a second dose administered after an interval of three weeks showed an increase in overall GMT from ~~333~~ **307** to ~~976~~ **873** (N=~~871~~**66**) and an increase in GMT from ~~237~~ **243** to ~~776~~ **733** in children who were seronegative at baseline (N=~~46~~**45**).

The seroprotection rate*, seroconversion rate* and the seroconversion factor for anti-HA antibody to H1N1 in infants aged 6-11 months by HI assay after administration of 7.5 µg of Focetria were as follows:**

Infants 6-11 months				
Anti-HA antibody	**21 days after 1st dose(day 22)**		**21 days after 2nd dose (day 43)**	
	Total N=57	**Seronegative at baseline N=37**	**Total N=57**	**Seronegative at baseline N=37**
Seroprotection rate (95% CI)	**100% (94-100)**	**100% (91-100)**	**100% (94-100)**	**100% (91-100)**
GMR (95% CI)	**21 (14-30)**	**32 (18-55)**	**128 (74-221)**	**274 (196-383)**
Seroconversion or Significant Increase (95% CI)	**96% (88-100)**	**100% (91-100)**	**98% (91-100)**	**100% (91-100)**

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

Data on responses to a second dose administered after an interval of three weeks showed an increase in overall GMT from 274 to 1700 (N=57) and an increase in GMT from 162 to 1399 in children who were seronegative at baseline (N=37).

~~**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 1st dose~~	~~21 days after 2nd 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 ≥ 25 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 1st dose	21 days after 2nd 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 ≥ 25 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 1st dose	21 days after 2nd 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 ≥ 25 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 1st dose	21 days after 2nd 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 ≥ 25 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 1st dose	21 days after 2nd 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 ≥ 25 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.

Additional information is available from the studies conducted with a vaccine similar in composition to Focetria but containing antigen derived from H5N1 viruses. Please consult the Product Information of Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted).

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

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

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

1.1.1 B. CONDITIONS OF THE MARKETING AUTHORISATION

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

(Manufacturer responsible for monovalent pooled harvests, before final filtration):
Novartis Vaccines and Diagnostics S.r.l.
Via Fiorentina, 1 – 53100 Siena
Italy

(Manufacturer responsible for final filtration of monovalent pooled harvest):
Novartis Vaccines and Diagnostics S.r.l.
Loc. Bellaria – 53018 Rosia – Sovicille (SI)
Italy

Name and address of the manufacturer(s) responsible for batch release

Novartis Vaccines and Diagnostics S.r.l.
Loc. Bellaria – 53018 Rosia – Sovicille (SI)
Italy

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

~~Focetria can only be marketed when there is an official WHO/EU declaration of an influenza pandemic, on the condition that the Marketing Authorisation Holder for Focetria takes due account of the officially declared pandemic strain.~~

CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- The MAH shall agree with Member States to measures facilitating the identification and traceability of the A/H1N1 ~~pandemic~~ vaccine administered to each patient, in order to minimise medication errors and aid patients and health care professionals to report adverse reactions. This may include the provision by the MAH of stickers with invented name and batch number with each pack of the vaccine.

- The MAH shall agree with Member States on mechanisms allowing patients and health care professionals to have continuous access to updated information regarding Focetria.

- The MAH shall agree with Member States on the provision of a targeted communication to healthcare professionals which should address the following:

    - The correct way to prepare the vaccine prior to administration.

    - Adverse events to be prioritised for reporting, i.e. fatal and life-threatening adverse reactions, unexpected severe adverse reactions, adverse events of special interest (AESI).

- The minimal data elements to be transmitted in individual case safety reports in order to facilitate the evaluation and the identification of the vaccine administered to each subject, including the invented name, the vaccine manufacturer and the batch number.

- If a specific notification system has been put in place, how to report adverse reactions.

- **OTHER CONDITIONS**

Official batch release: in accordance with Article 114 Directive 2001/83/EC as amended, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 11.1 (dated 05 January 2010) presented in Module 1.8.1 of the marketing authorisation application, is in place and functioning before the product is placed on the market and for as long as the marketed product remains in use.

PSUR submission: ~~during the influenza pandemic:~~
~~During a pandemic situation, the frequency of submission of periodic safety update reports specified in Article 24 of Regulation (EC) No 726/2004 will not be adequate for the safety monitoring of a pandemic vaccine for which high levels of exposure are expected within a short period of time. Such situation requires rapid notification of safety information that may have the greatest implications for benefit-risk balance in a pandemic. Prompt analysis of cumulative safety information, in light of the extent of exposure, will be crucial for regulatory decisions and protection of the population to be vaccinated.~~
~~The MAH shall submit on a monthly basis a simplified periodic safety update report with the timelines, format and content as defined in the CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine (EMEA/359381/2009) and any subsequent update.~~
The marketing Authorisation holder will submit periodic safety update reports on a 6-month cycle unless the CHMP decides otherwise.

Risk Management plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version RMPv1.3 (dated 18 September 2009) of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

~~C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER~~

~~The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame, the results of which shall form the basis of the continuous reassessment of the benefit/risk profile.~~

~~Clinical~~	~~The MAH commits to provide abridged report for the following study performed in children:~~ ~~Safety and immunogenicity data:~~ ~~Study V111_03~~ ~~- post vaccination 2 cohort 4 (children 6-11 months)~~	~~26 March 2010~~

~~Clinical~~	~~The MAH commits to provide the results of the effectiveness study.~~	~~Results of study to be provided within two weeks of availability.~~
~~Pharmacovigilance~~	~~The MAH will submit the results of a prospective cohort safety study in at least 9,000 patients in different age groups, including immunocompromised subjects, in accordance with the protocol submitted with the Risk Management Plan. Observed-to-Expected analyses will be performed.~~	~~Interim and final results will be submitted in accordance with the protocol.~~
~~Pharmacovigilance~~	~~The MAH commits to submit the results of a study in a pregnancy registry.~~	~~Results to be provided in the simplified PSUR.~~

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARDBOARD BOX FOR SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Focetria suspension for injection in pre-filled syringe
~~Pandemic~~ Influenza vaccine **(H1N1)v** (surface antigen, inactivated, adjuvanted)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose of 0.5 ml contains: Active Ingredients: Influenza virus surface antigens (haemagglutinin and neuraminidase), propagated in eggs, and adjuvanted with MF59C.1, of strain:

A/California/**0**7/2009 (H1N1)~~v like~~ **- derived** strain **used NYMC** ~~(~~X-181~~)~~ 7.5 micrograms** per 0.5 ml dose

Adjuvant: MF59C.1 oil in water emulsion containing squalene, as the oil phase, stabilised with polysorbate 80 and sorbitan trioleate in a citrate buffer.

3. 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.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.

1 x single dose of 0.5 ml pre-filled syringe
10 x single dose of 0.5 ml pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

To be administered intramuscularly into the deltoid muscle.

Warning: Do not inject intravascularly.

Read the package leaflet before use.

The vaccine should be allowed to reach room temperature before use. Gently shake before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/385/001
EU/1/07/385/002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARDBOARD BOX FOR 10-DOSE VIAL

1. NAME OF THE MEDICINAL PRODUCT

Focetria suspension for injection in multidose container
~~Pandemic~~ Influenza vaccine **(H1N1)v** (surface antigen, inactivated, adjuvanted)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose of 0.5 ml contains: Active Ingredients: Influenza virus surface antigens (haemagglutinin and neuraminidase), propagated in eggs, and adjuvanted with MF59C.1, of strain:

A/California/**0**7/2009 (H1N1)~~v like~~ **- derived** strain **used NYMC** ~~(~~X-181~~)~~ 7.5 micrograms** per 0.5 ml dose

Adjuvant: MF59C.1 oil in water emulsion containing squalene, as the oil phase, stabilised with polysorbate 80 and sorbitan trioleate in a citrate buffer.

3. 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.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
Vials
10 x 10 doses of 0.5 ml vaccine (5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

To be administered intramuscularly into the deltoid muscle.

Warning: Do not inject intravascularly.

Read the package leaflet before use.

The vaccine should be allowed to reach room temperature before use. Gently shake before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local requirements

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/385/004

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL FOR SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Focetria injection
~~Pandemic~~ Influenza vaccine **(H1N1)v**
Intramuscular use

2. METHOD OF ADMINISTRATION

Shake before use.

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

Store in a refrigerator.
Novartis V&D S.r.l.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL FOR 10-DOSE VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Focetria injection
~~Pandemic~~ Influenza vaccine **(H1N1)v**
Intramuscular use.

2. METHOD OF ADMINISTRATION

Gently shake before use.

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Multidose vial (5 ml)

6. OTHER

Store in a refrigerator.
Novartis V&D S.r.l.

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Focetria suspension for injection
~~Pandemic~~ Influenza vaccine **(H1N1)v** (surface antigen, inactivated, adjuvanted)

~~For the most up-to-date information please consult the website of the European Medicines Agency (EMA): http://www.ema.europa.eu/~

Read all of this leaflet carefully before you receive this vaccine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

1. WHAT FOCETRIA IS AND WHAT IT IS USED FOR

Focetria is a vaccine to prevent ~~pandemic~~ influenza (flu) **caused by A(H1N1) 2009 virus.**

~~Pandemic flu is a type of influenza that occurs every few decades and which spreads rapidly around the world. The symptoms of pandemic flu are similar to those of an ordinary flu but may be more severe.~~

When a person is given the vaccine, the immune system (the body's natural defence system) will produce its own protection (antibodies) against the disease. None of the ingredient in the vaccine can cause flu.

2. BEFORE YOU RECEIVE FOCETRIA

You should not receive Focetria:

- if you have previously had a sudden life-threatening allergic reaction to any ingredient of Focetria (these are listed at the end of the leaflet) or to any of the substances that may be present in trace amounts as follows: egg and chicken protein, ovalbumin, formaldehyde, kanamycin and neomycin sulphate (antibiotics) or cetyltrimethylammonium bromide (CTAB). Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue. ~~However, in a pandemic situation, it may be appropriate for you to have the vaccine provided that appropriate medical treatment is immediately available in case of an allergic reaction.~~

If you are not sure, talk to your doctor or nurse before having this vaccine.

Take special care with Focetria:
- if you have had any allergic reaction other than a sudden life-threatening allergic reaction to any ingredient contained in the vaccine, to thiomersal (only for the multidose vial presentation), to egg and, chicken protein, ovalbumin, formaldehyde, kanamycin and neomycin sulphate (antibiotics) or cetyltrimethylammonium bromide (CTAB). (see section 6. Further information).

- if you have a severe infection with a high temperature (over 38°C). If this applies to you then your vaccination will usually be postponed until you are feeling better. A minor infection such as a cold

should not be a problem, but your doctor or nurse should advise whether you could still be vaccinated with Focetria,

- if you are having a blood test to look for evidence of infection with certain viruses. In the first few weeks after vaccination with Focetria the results of these tests may not be correct. Tell the doctor requesting these tests that you have recently been given Focetria.

In any of these cases, TELL YOUR DOCTOR OR NURSE, as vaccination may not be recommended, or may need to be delayed.

Please inform your doctor or nurse if you have a bleeding problem or bruise easily.

Taking other medicines

Please tell your doctor or nurse if you are taking or have recently taken any other medicines, including medicines obtained without a prescriptionor have recently been given any other vaccine.
Focetria can be given at the same time as non-adjuvanted seasonal influenza vaccines, with injections made into separate limbs.

There is no information on administration of the vaccine Focetria with any other vaccines. However, if this cannot be avoided, the vaccines should be injected into separate limbs. In such cases, you should be aware that the side effects may be more intense.

Pregnancy and breast-feeding

Tell your doctor if you are pregnant, think you may be pregnant, plan to become pregnant. You should discuss with your doctor whether you should receive Focetria.
The vaccine may be used during breast-feeding.

Driving and using machines

Some effects mentioned under section 4. “Possible side effects” may affect the ability to drive or use machines.

Important information about some of the ingredients of Focetria

This vaccine in a multi-dose vial contains thiomersal as a preservative and it is possible that you may experience an allergic reaction. Tell your doctor if you have any known allergies.
This medicinal contains less than 1 mmol sodium (23 mg) and less than 1 mmol of potassium (39 mg) per 0.5 ml dose, i.e. essentially sodium- and potassium free.

3. HOW FOCETRIA IS GIVEN

Your doctor or nurse will administer the vaccine in accordance with official recommendations.
The vaccine will be injected into a muscle (usually in the upper arm).

Adults
A dose (0.5 ml) of the vaccine will be given.
Clinical data 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:
A dose (0.5 ml) of the vaccine and a second dose of 0.5 ml at least three weeks later.

Children and adolescents 3-17 years of age:

You or your child will receive one dose of 0.5 ml vaccine.
Available clinical data 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 6 months to 35 months:
You or your child will receive one dose of 0.5 ml vaccine. ~~and a second dose of 0.5 ml at least three weeks later.~~
If a second dose is administered there should be an interval of at least three weeks between the first and second dose.

Children aged less than 6 months of age:
Vaccination is currently not recommended in this age group.

When Focetria is given for the first dose, it is recommended that Focetria (and not another vaccine against H1N1) be given for the complete vaccination course.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Focetria can cause side effects, although not everybody gets them.
Allergic reactions may occur following vaccination, in rare cases leading to shock. Doctors are aware of this possibility and have emergency treatment available for use in such cases.

In the clinical studies with the vaccine, most side effects were mild in nature and short term. The side-effects are generally similar to those related to the seasonal flu vaccine.

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)

The side effects listed below have occurred with Focetria in clinical studies in adults, including the elderly:

Very common:
Pain, hardening of the skin at the injection site, injection site redness, injection site swelling, pain at the site of injection, aching muscles, headache, sweating, fatigue, generally feeling unwell and shivering

Common:
Bruising of the skin at the injection site, fever and nausea

Uncommon:
Flu like symptoms

Rare:
Convulsion, eye swelling and anaphylaxis

These side effects usually disappear within 1-2 days without treatment. If they persist, CONSULT YOUR DOCTOR.

Side effects from clinical studies in children

A clinical study was conducted with ~~a similar~~ **the same** vaccine in children. General side effects 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: ~~generally feeling unwell, aching muscles, pain, headache, fatigue,~~ sweating, nausea and chills. **Very commonly reported reactions in both children and adolescents were pain, hardening of the skin at the injection site, injection site redness, generally feeling unwell, muscle ache, headache and fatigue.**

Other side effects

The side effects listed below have occurred in the days or weeks after vaccination with Focetria.

Generalised skin reactions including itching, urticaria (hives), rash or swelling of the skin and mucous membranes.
Disorders of the gut such as nausea, vomiting, abdominal pain and diarrhoea.
Headache, dizziness, drowsiness, fainting.
Neurological disorders such as severe stabbing or throbbing pain along one or more nerves, tingling, fits, and neuritis (inflammation of nerves).
Swollen lymph nodes, palpitations, weakness, pain in the extremities and cough.
Allergic reactions possibly with shortness of breath, wheezing, swelling of the throat, or leading to a dangerous decrease of blood pressure, which, if untreated, may lead to shock. Doctors are aware of this possibility and have emergency treatment available for use in such cases.

~~Data for children and adolescents who received Focetria showed a comparable safety profile. Very commonly reported reactions were pain, hardening of the skin at the injection site, injection site redness, generally feeling unwell, myalgia, headache and fatigue.~~

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

In addition, the side effects listed below have occurred in the days or weeks after vaccination with adjuvanted and non-adjuvanted vaccines given routinely every year to prevent flu. These side effects may occur with Focetria.

Rare:
Low blood platelet count which can result in bleeding or bruising.

Very rare:
Vasculitis (inflammation of the blood vessels which can cause skin rashes, joint pain and kidney problems), exudative erythema multiforme.
Neurological disorders such as encephalomyelitis (inflammation of the central nervous system), and a type of paralysis known as Guillain-Barré Syndrome.

If any of these side effects occur, please tell your doctor or nurse immediately.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE FOCETRIA

Keep out of the reach and sight of children.

Do not use Focetria after the expiry date which is stated on the carton and the label. The expiry date refers to the last day of that month.

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

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Focetria contains

- Active Substance:
  Influenza virus surface antigens (haemagglutinin and neuraminidase)* of strain:
  A/California/**0**7/2009 (H1N1)~~v like~~ **- derived** strain **used NYMC** ~~(~~X-181~~)~~ 7.5 micrograms** per 0.5 ml dose

  * propagated in eggs
  ** expressed in microgram haemagglutinin.

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

- Adjuvant:
  The vaccine contains an 'adjuvant' (MF59C.1) to stimulate a better response. MF59C.1 is an oil/water emulsion containing 9.75 mg squalene, 1.175 mg polysorbate 80 and 1.175 mg sorbitan trioleate in a citrate buffer. Quantities are expressed per 0.5 ml vaccine dose.

- Other Ingredients:
  The other ingredients are: thiomersal (multidose vial only), sodium chloride, potassium chloride, potassium dihydrogen phosphate, disodium phosphate dihydrate, magnesium chloride hexahydrate, calcium chloride dihydrate, sodium citrate, citric acid and water for injections.

What Focetria looks like and contents of the pack
Focetria is a milky-white liquid.
It is provided in:
- a ready-to-use syringe, containing a single dose of 0.5 ml for injection;
- vial containing ten doses of 0.5 ml each for injection.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Novartis Vaccines and Diagnostics S.r.l.
Via Fiorentina, 1 – Siena,
Italy.

Manufacturer
Novartis Vaccines and Diagnostics S.r.l.
Loc. Bellaria
53018 Rosia
Sovicille (SI)
Italy.

The following information is intended for medical or healthcare professionals only:

Instructions for administration of the vaccine:

Ready-to-use syringe, containing a single dose of 0.5 ml for injection:

The vaccine should be allowed to reach room temperature before use.
Gently shake before use.

Vial containing ten doses (0.5 ml each) for injection:

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 to 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.

The vaccine should not be administered intravascularly.

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

This leaflet was last approved in {MM/YYYY}.

~~Focetria has been authorised under "Exceptional Circumstances". The European Medicines Agency (EMA) will regularly review any new information on the medicine and this package leaflet will be updated as necessary.~~

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: http://www.ema.europa.eu/