

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Focetria suspension for injection in pre-filled syringe
Influenza vaccine H1N1v (surface antigen, inactivated, adjuvanted)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

A/California/07/2009 (H1N1)-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

For the 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 (H1N1v) 2009 virus (see section 4.4).
Focetria 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 data from clinical studies in healthy subjects.

Posology

Adults (18-60 years):

One dose of 0.5 ml at an elected date.

Immunogenicity data obtained at three weeks after one dose of Focetria H1N1v 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.

Paediatric population

Children and adolescents aged 3-17 years:

One dose of 0.5 ml at an elected date.

Immunogenicity data obtained at three weeks after one dose of Focetria H1N1v 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 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.

Children aged less than 6 months:

No data are available in children aged less than 6 months (see sections 4.8 and 5.1).

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 H1N1v (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.

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

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

Immunisation should be postponed in patients with severe febrile illness or acute infection.

Focetria should under no circumstances be administered intravascularly.

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

Cases of convulsion with and without fever have been reported in subjects vaccinated with Focetria. The majority of febrile convulsions occurred in paediatric subjects. Some cases were observed in subjects with a history of epilepsy. Particular attention should be given to subjects suffering from epilepsy and the physician should inform the subjects (or parents) about the possibility to experience convulsion. (See section 4.8).

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 H1N1v vaccines.

4.5 Interaction with other medicinal products and other forms of interaction

Focetria H1N1v may be co-administered with a non adjuvanted seasonal influenza vaccine. Data on co-administration of Focetria H1N1v 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 Fertility, pregnancy and lactation

Pregnancy

Safety data are available in pregnant women exposed to Focetria in particular during second and third trimesters. Postmarketing spontaneously reported adverse events, an interventional study and large observational studies do not suggest direct or indirect harmful effects of Focetria exposure on pregnancy. Further, data from vaccinations with seasonal inter-pandemic inactivated trivalent vaccines in pregnant women do not indicate that adverse foetal and maternal outcomes were attributable to the vaccine. Health care providers need to assess the benefits and potential risks of administering Focetria vaccine to pregnant women, taking into consideration official recommendations.

Breast-feeding

Focetria may be administered to lactating women.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

- Clinical trials

Adverse reactions reported are listed according to the following frequency:

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

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

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

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

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

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

Adult and Elderly

In a clinical trial 131 adults and 123 elderly were exposed to two doses of the 7.5 μg Focetria. 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.

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

Nervous system disorders

Very common: headache

Rare: convulsions

Skin and subcutaneous tissue disorders

Common: sweating

Uncommon: urticaria

Rare: eye swelling

Musculoskeletal, connective tissue and bone disorders

Very common: myalgia

Common: arthralgia

Gastrointestinal disorders

Common: nausea

General disorders and administration site conditions

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

Common: injection site ecchymosis and fever

Uncommon: influenza like illness

Rare: anaphylaxis

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

Paediatric population

Children and adolescents 6 months to 17 years of age

Clinical trials with Focetria H1N1v

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

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

	Injection 1	Injection 2
Children (3 to 8 years of age)	N=87	N=85
Any adverse reaction	67%	61%
Local	56%	49%
Systemic	32%	31%
Fever $\geq 38^{\circ}\text{C}$ to 38.9°C	3%	1%
Fever 39°C to 39.9°C	0%	1%
Fever $\geq 40^{\circ}\text{C}$	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 $\geq 38^{\circ}\text{C}$ to 38.9°C	2%	1%
Fever 39°C to 39.9°C	0%	0%
Fever $\geq 40^{\circ}\text{C}$	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 $\geq 38^{\circ}\text{C}$ to 38.9°C	9%	6%
Fever 39°C to 39.9°C	2%	4%
Fever $\geq 40^{\circ}\text{C}$	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 $\geq 38^{\circ}\text{C}$ to 38.9°C	10%	11%
Fever 39°C to 39.9°C	4%	1%
Fever $\geq 40^{\circ}\text{C}$	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.

Very common reactions reported in 233 infants and toddlers 6 to 35 months of age: Tenderness, erythema, irritability, unusual crying, sleepiness, diarrhoea and change in eating habits. Induration was a common reaction in toddlers but was less common in infants.

- Post-marketing surveillance

Focetria H1N1v

In addition to the adverse reactions reported in the clinical trials, the following have been reported during post-marketing experience with Focetria H1N1v:

Blood and lymphatic system disorders

Lymphadenopathy.

Cardiac disorders

Palpitation, tachycardia.

General disorders and administration site conditions

Asthenia.

Musculoskeletal, connective tissue and bone disorders

Muscular weakness, pain in extremities.

Respiratory disorders

Cough.

Skin and subcutaneous tissue disorders

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

Gastrointestinal disorders

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

Nervous system disorders

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

Immune system disorders

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

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

Rare:

Transient thrombocytopenia.

Very rare:

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

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines. Influenza vaccine, ATC Code: J07BB02

Clinical efficacy and safety

Clinical studies with Focetria H1N1v currently provide:

- Safety and immunogenicity data obtained after administration of one or two doses of Focetria H1N1v to healthy children and adolescents aged 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 H1N1v

- Studies in adults and elderly:

Immunogenicity results with two doses of 7.5 µg Focetria H1N1v 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/H1N1v in adult and elderly subjects by HI assay after administration of 7.5 µg of Focetria were as follows:

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

* measured by HI assay

** geometric mean ratios of HI

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

- Paediatric population

The seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibody to H1N1v in children and adolescents aged 9-17 years by HI assay after administration of 7.5 µg of Focetria were as follows:

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

* measured by HI assay

** geometric mean ratios of HI

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 H1N1v in children aged 3-8 years by HI assay after administration of 7.5 µg of Focetria were as follows:

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

* 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 H1N1v in children aged 12-35 months by HI assay after administration of 7.5 µg of Focetria were as follows:

Children 12-35 months				
Anti-HA antibody	21 days after 1 st dose(day 22)		21 days after 2 nd 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)

* 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 307 to 873 (N=66) and an increase in GMT from 243 to 733 in children who were seronegative at baseline (N=45).

The seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibody to H1N1v 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 1 st dose(day 22)		21 days after 2 nd 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).

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

12 August 2010

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
Influenza vaccine H1N1v (surface antigen, inactivated, adjuvanted)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

A/California/07/2009 (H1N1)-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
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This is a multidose container.

See section 6.5 for the number of doses per vial.

For the 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(H1N1v) 2009 virus (see section 4.4).
Focetria 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 data from clinical studies in healthy subjects.

Posology

Adults (18-60 years):

One dose of 0.5 ml at an elected date.

Immunogenicity data obtained at three weeks after one dose of Focetria H1N1v 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.

Paediatric population

Children and adolescents aged 3-17 years:

One dose of 0.5 ml at an elected date.

Immunogenicity data obtained at three weeks after one dose of Focetria H1N1v 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 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.

Children aged less than 6 months:

No data are available in children aged less than 6 months (see sections 4.8 and 5.1).

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 H1N1v (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.

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

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

Immunisation should be postponed in patients with severe febrile illness or acute infection.

Focetria should under no circumstances be administered intravascularly.

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

Cases of convulsion with and without fever have been reported in subjects vaccinated with Focetria. The majority of febrile convulsions occurred in paediatric subjects. Some cases were observed in subjects with a history of epilepsy. Particular attention should be given to subjects suffering from epilepsy and the physician should inform the subjects (or parents) about the possibility to experience convulsion. (See section 4.8).

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 H1N1v vaccines.

4.5 Interaction with other medicinal products and other forms of interaction

Focetria H1N1v may be co-administered with a non adjuvanted seasonal influenza vaccine. Data on co-administration of Focetria H1N1v 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 Fertility, pregnancy and lactation

Pregnancy

Safety data are available in pregnant women exposed to Focetria in particular during second and third trimesters. Postmarketing spontaneously reported adverse events, an interventional study and large observational studies do not suggest direct or indirect harmful effects of Focetria exposure on pregnancy. Further, data from vaccinations with seasonal inter-pandemic inactivated trivalent vaccines in pregnant women do not indicate that adverse foetal and maternal outcomes were attributable to the vaccine. Health care providers need to assess the benefits and potential risks of administering Focetria vaccine to pregnant women, taking into consideration official recommendations.

Breast-feeding

Focetria may be administered to lactating women.

Fertility

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

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

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

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

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

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

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

Adults and elderly

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

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

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

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

Adverse reactions from clinical trials with the mock-up vaccine are listed below.

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

Nervous system disorders

Very common: headache

Rare: convulsions

Skin and subcutaneous tissue disorders

Common: sweating

Uncommon: urticaria

Rare: eye swelling

Musculoskeletal, connective tissue and bone disorders

Very common: myalgia

Common: arthralgia

Gastrointestinal disorders

Common: nausea

General disorders and administration site conditions

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

Common: injection site ecchymosis and fever

Uncommon: influenza like illness

Rare: anaphylaxis

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

Paediatric population

Children and adolescents 6 months to 17 years of age

Clinical trials with Focetria H1N1v

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

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

	Injection 1	Injection 2
Children (3 to 8 years of age)	N=87	N=85
Any adverse reaction	67%	61%
Local	56%	49%
Systemic	32%	31%
Fever $\geq 38^{\circ}\text{C}$ to 38.9°C	3%	1%
Fever 39°C to 39.9°C	0%	1%
Fever $\geq 40^{\circ}\text{C}$	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 $\geq 38^{\circ}\text{C}$ to 38.9°C	2%	1%
Fever 39°C to 39.9°C	0%	0%
Fever $\geq 40^{\circ}\text{C}$	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 $\geq 38^{\circ}\text{C}$ to 38.9°C	9%	6%
Fever 39°C to 39.9°C	2%	4%
Fever $\geq 40^{\circ}\text{C}$	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 $\geq 38^{\circ}\text{C}$ to 38.9°C	10%	11%
Fever 39°C to 39.9°C	4%	1%
Fever $\geq 40^{\circ}\text{C}$	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.

Very common reactions reported in 233 infants and toddlers 6 to 35 months of age: Tenderness, erythema, irritability, unusual crying, sleepiness, diarrhoea and change in eating habits. Induration was a common reaction in toddlers but was less common in infants.

- Post-marketing surveillance

Focetria H1N1v

In addition to the adverse reactions reported in the clinical trials, the following have been reported during post-marketing experience with Focetria H1N1v:

Blood and lymphatic system disorders

Lymphadenopathy.

Cardiac disorders

Palpitation, tachycardia.

General disorders and administration site conditions

Asthenia.

Musculoskeletal, connective tissue and bone disorders

Muscular weakness, pain in extremities.

Respiratory disorders

Cough.

Skin and subcutaneous tissue disorders

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

Gastrointestinal disorders

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

Nervous system disorders

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

Immune system disorders

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

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

Rare:

Transient thrombocytopenia.

Very rare:

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

Thiomersal:

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

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines. Influenza vaccine, ATC Code: J07BB02

Clinical efficacy and safety

Clinical studies with Focetria H1N1v currently provide:

- Safety and immunogenicity data obtained after administration of a one or two doses of Focetria H1N1v to healthy children and adolescents aged 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 H1N1v

- Studies in adults and elderly

Immunogenicity results with two doses of 7.5 µg Focetria H1N1v 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/H1N1v in adult and elderly subjects by HI assay after administration of 7.5 µg of Focetria were as follows:

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

* measured by HI assay

** geometric mean ratios of HI

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

- Paediatric population

The seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibody to H1N1v in children and adolescents aged 9-17 years by HI assay administration of 7.5 µg of Focetria were as follows:

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

* measured by HI assay

** geometric mean ratios of HI

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 H1N1v in children aged 3-8 years by HI assay after administration of 7.5 µg of Focetria were as follows:

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

* 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 H1N1v in children aged 12-35 months by HI assay after administration of 7.5 µg of Focetria were as follows:

Anti-HA antibody	Children 12-35 months			
	21 days after 1 st dose(day 22)		21 days after 2 nd 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)

* 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 307 to 873 (N=66) and an increase in GMT from 243 to 773 in children who were seronegative at baseline (N=45).

The seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibody to H1N1v 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 1 st dose(day 22)		21 days after 2 nd 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).

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.

Data are 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

12 August 2010

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**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE
MARKETING AUTHORISATION**

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.

- The MAH shall agree with Member States to measures facilitating the identification and traceability of the A/H1N1 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.
- **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.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before the product is placed on the market and for as long as the marketed product remains in use.

Risk Management plan (RMP)

The MAH shall perform the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR). In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

PSURs

The PSUR cycle for the medicinal product should follow a half-yearly cycle until otherwise agreed by the CHMP

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

Not applicable.

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
Influenza vaccine H1N1v (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/07/2009 (H1N1)-derived strain used NYMC X-181 7.5 micrograms haemagglutinin

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
Influenza vaccine H1N1v (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/07/2009 (H1N1)-derived strain used NYMC X-181 7.5 micrograms haemagglutinin

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
Influenza vaccine H1N1v
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
Influenza vaccine H1N1v
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

Influenza vaccine H1N1v (surface antigen, inactivated, adjuvanted)

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.

- 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, talk to your doctor. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Focetria is and what it is used for
2. What you need to know before you receive Focetria
3. How Focetria is given
4. Possible side effects
5. How to store Focetria
6. Contents of the pack and other information

1. What FOCETRIA is and what it is used for

Focetria is a vaccine to prevent influenza (flu) caused by A(H1N1v) 2009 virus.

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. What you need to know before you receive FOCETRIA

Do 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.

Warnings and precautions

Talk to your doctor or nurse before receiving Focetria

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.

The physician should inform you about the possibility to experience convulsion, in particular if you have had previous history of epilepsy.

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.

Other medicines and Focetria

Tell your doctor or nurse if you are taking or have recently taken any other medicines, including medicines obtained without a prescription or 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 taking into consideration official recommendation based on post-marketing reported adverse events during second and third trimesters of pregnancy.

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.

Focetria contains

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.

Use in children and adolescents

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.

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 H1N1v) 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 side effects listed below have occurred with Focetria in clinical studies in adults, including the elderly:

Very common (affects more than 1 user in 10):

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 (affects 1 to 10 users in 100):

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

Uncommon (affects 1 to 10 users in 1,000):

Flu like symptoms

Rare (affects 1 to 10 users in 10,000):

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 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. Among the adolescents the very common events were: 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 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 you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store FOCETRIA

Keep this medicine out of the sight and reach 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. Contents of the pack and other information

What Focetria contains

- The active substance is:
Influenza virus surface antigens (haemagglutinin and neuraminidase)* of strain:
A/California/07/2009 (H1N1)-derived strain
used NYMC X-181 7.5 micrograms** per 0.5 ml dose

* propagated in eggs
** expressed in microgram haemagglutinin.
- 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.
- The other ingredients are:
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.

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

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

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

Instructions for administration of the vaccine:

The vaccine should not be administered intravascularly.

Pre-filled syringe:

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.

Multidose vial:

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.

Data are 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.

ANNEX IV

**SCIENTIFIC CONCLUSIONS AND GROUNDS RECOMMENDING THE VARIATION
TO THE TERMS OF THE MARKETING AUTHORISATION**

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for Focetria, the scientific conclusions of PRAC are as follows:

Based on the findings of an observational study conducted in >2000 pregnant women, reflecting the use of Focetria in pregnant women, influenza A (H1N1) vaccination with Focetria does not seem to be associated with an increased risk of adverse pregnancy outcomes, especially in the second or third trimesters of pregnancy. Therefore, the relevant SmPC wording currently stating the limited availability of clinical data in pregnant women, is recommended to be changed to reflect the newly available information.

Therefore, in view of available data regarding the use of Focetria during pregnancy, the PRAC considered that changes to the product information were warranted. The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds recommending the variation to the terms of the Marketing Authorisation

On the basis of the scientific conclusions for Focetria, the CHMP is of the opinion that the benefit-risk balance of the medicinal product containing the active substance influenza vaccine h1n1v (surface antigen, inactivated, adjuvanted) is favourable subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation should be varied.