

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Foclivia suspension for injection in pre-filled syringe
Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

A/Vietnam/1194/2004 (H5N1) 7.5 micrograms**
per 0.5 ml dose

* propagated in fertilised hens' eggs from healthy chicken flocks

** expressed in microgram haemagglutinin.

Adjuvant MF59C.1 containing:

Squalene	9.75 milligrams
Polysorbate 80	1.175 milligrams
Sorbitan trioleate	1.175 milligrams
Sodium citrate	0.66 milligrams
Citric acid	0.04 milligrams

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

Excipient with known effect:

The vaccine contains 1.899 milligrams of sodium and 0.081 milligrams of potassium per 0.5 ml dose.

Foclivia may contain trace residues of egg and chicken proteins, ovalbumin, kanamycin sulphate, neomycin sulphate, formaldehyde and cetyltrimethylammonium bromide which are used during the manufacturing process (see section 4.3).

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 in an officially declared pandemic situation.
Foclivia should be used in accordance with Official Guidance.

4.2 Posology and method of administration

Posology

Adults and elderly (18 years of age and above): 0.5 ml at an elected date.
A second dose of vaccine should be given after an interval of at least 3 weeks.

Foclivia was evaluated in adults (aged 18 to 60 years old) and elderly (over 60 years old) following a 1, 22 day primary vaccination schedule.

Data on a third dose (booster) administered 6 months after the first dose are limited (see sections 4.8 and 5.1).

Paediatric population

The safety and efficacy of Foclivia in subjects under 18 years of age have not yet been established. Currently available data in subjects aged 6 months to 18 years of age are described in section 5.1 but no recommendation on a posology can be made.

No data are available in children aged less than 6 months.

Method of administration

Immunisation should be carried out by intramuscular injection 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 (eggs, chicken proteins, ovalbumin, kanamycin sulphate, neomycin sulphate, formaldehyde and cetyltrimethylammonium bromide) of this vaccine.

However, in a pandemic situation, it may be appropriate to give this vaccine to individuals with a history of anaphylaxis as defined above, provided that facilities for resuscitation are immediately available in case of need. See section 4.4.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Caution is needed when administering this vaccine to persons with a known hypersensitivity to the active substance, to any of the excipients listed in section 6.1 and to residues (eggs, chicken proteins, ovalbumin, kanamycin sulphate, neomycin sulphate, formaldehyde and cetyltrimethylammonium bromide).

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

If the pandemic situation allows, immunisation should be postponed in patients with febrile illness until the fever is resolved.

The vaccine should under no circumstances be administered intravascularly or intradermally. There are no data with Foclivia using the subcutaneous route of administration. 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 bleeding.

Protection against influenza

There is no immune correlate of protection established for influenza A (H5N1).

A protective immune response may not be elicited in all vaccine recipients. In addition, antibody responses in patients with endogenous or iatrogenic immunosuppression may be insufficient to provide protection.

Some degree of cross-reactive immunity has been observed against H5N1 viruses of clades different to that of the vaccine strain. However, the degree of protection that may be elicited to H5N1 strains of other clades is unknown (see section 5.1).

Since a second dose is recommended, it should be noted that there are no safety, immunogenicity or efficacy data to support interchangeability of Foclivia with other H5N1 monovalent vaccines.

While no data are available from the use of Foclivia, cases of convulsion with and without fever have been reported in subjects vaccinated with Focetria, an MF59.1 adjuvanted H1N1 pandemic vaccine similar to Foclivia.

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).

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

4.5 Interaction with other medicinal products and other forms of interaction

Foclivia may be co-administered with non-adjuvanted seasonal influenza vaccines, and immunisation should be carried out on separate limbs.

There are no data on co-administration of Foclivia with vaccines other than non-adjuvanted seasonal influenza 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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Limited data obtained from women who became pregnant during the course of clinical trials with Foclivia or other pandemic vaccines adjuvanted with MF59C.1 were insufficient to inform vaccine-associated risks in pregnancy.

However, it is estimated that during the 2009 H1N1 pandemic more than 90,000 women were vaccinated during pregnancy with Focetria (an H1N1 pandemic vaccine similar to Foclivia) which contains the same amount of MF59C.1 as Foclivia. Post-marketing spontaneously reported adverse events and an interventional study do not suggest direct or indirect harmful effects of Focetria exposure on pregnancy. In addition, two large observational studies designed to assess the safety of Focetria exposure in pregnancy showed no increase in the rates of gestational diabetes, preeclampsia, abortions, stillbirth, low birth weight, prematurity, neonatal deaths, and congenital malformations among almost 10,000 vaccinated pregnant women and their offspring compared with unvaccinated controls.

Health care providers need to assess the benefits and potential risks of administering Foclivia vaccine to pregnant women, taking into consideration official recommendations.

Breast-feeding

There are no data regarding the use of Foclivia during breast-feeding. The potential benefits and risks to the mother and infant should be considered before administering Foclivia.

Fertility

There are no data concerning human fertility. A study in female rabbits did not indicate reproductive or developmental toxicity of Foclivia. Male fertility has not been assessed in animals (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

- Clinical trials

Adverse reactions from clinical trial in adults and elderly (above 18 years old)

The incidence of adverse reactions has been evaluated in seven clinical trials in healthy subjects involving over 4300 adults and elderly receiving H5N1 vaccine combined with MF59C.1 adjuvant (at least 7.5 µg haemagglutinin, HA) containing either the A/turkey/Turkey/1/2005 or the A/Vietnam/1194/2004 strain. There were 3872 subjects 18-60 years of age, 365 subjects 61-70 years of age, and 89 subjects greater than 70 years of age. The safety profile across clinical trials using H5N1 vaccine containing either the A/turkey/Turkey/1/2005 or the A/Vietnam/1194/2004 strain is comparable (see section 5.1). Clinical trials in 80 subjects receiving adjuvanted vaccine with an H5N3 or an H9N2 strain showed a similar safety profile.

Across all trials, there was a general trend towards decreased reports of solicited local adverse reactions after the second vaccination compared with the first.

Irrespective of antigen dose, almost all solicited systemic adverse reactions were reported on the day of vaccination (day 1) or during the 3 days immediately following.

Data on safety of a booster dose are limited to three trials performed with H5N1 MF59C.1 adjuvanted vaccine containing A/Vietnam/1194/2004 (V87P1, V87P2) or A/turkey/Turkey/1/2005 (V87P1E1) that included 116 adults (18-60 years) and 56 elderly subjects (≥61 years). No increase in solicited adverse reactions was reported when a booster dose was administered 6 or 18 months after the initial dosing series. A slight increase in solicited adverse reactions in adults was reported when a booster dose was administered 18 months after the initial dosing series. In the elderly, the reported solicited adverse reactions increased with the third booster dose only when compared with the second dose.

Tabulated list of adverse reactions

The adverse reaction rates reported after any vaccination dose (i.e. 1st, 2nd or booster) were similar and are listed according to the following MedDRA frequency convention and system organ class: 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).

MedDRA System Organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Rare (≥1/10,000 to <1/1,000)
Nervous system disorders	Headache		
Gastrointestinal disorders		Nausea	
Skin and subcutaneous tissue disorders		Sweating	
Musculoskeletal and connective tissue disorders	Myalgia	Arthralgia	

General disorders and administration site conditions	Injection site swelling, Injection site pain, Injection site induration, Injection site redness, Fatigue, Chills, Malaise	Injection site ecchymosis, Fever	Anaphylaxis
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The majority of these reactions usually disappear within 1-2 days without treatment.

Clinical trials in special populations

Adverse reactions in special populations have been evaluated in two clinical trials, V87_25 and V87_26, involving adult (18-60 years) and elderly (≥ 61 years) subjects who were either healthy or with underlying medical conditions or immunosuppressive conditions.

H5N1 MF59C.1 adjuvanted A/turkey/Turkey/1/2005 vaccine								
Study V87_25					Study V87_26			
	Medical conditions		Healthy		Immunocompromised		Healthy	
	Adults (20-60 years)*	Elderly (61-84 years)*	Adults (19-60 years)*	Elderly (61-79 years)*	Adults (20-60 years)*	Elderly (61-84 years)*	Adults (18-59 years)*	Elderly (61-91 years)*
No. of subjects	N=145	N=149	N=59	N=58	N=147	N=148	N=58	N=62

*actual age range of population enrolled

Across studies V87_25 and V87_26, the safety of H5N1 A/turkey/Turkey/1/2005 in healthy adult and elderly subjects was consistent with existing safety data from previous clinical trials. However, in immunocompromised subjects 18 through 60 years of age, slightly higher rates of nausea (13.0%) were reported. In addition, higher rates of arthralgia (up to 23.3%) were reported in both adult and elderly subjects, who were immunocompromised or with underlying medical conditions.

The following solicited adverse reactions were additionally collected in these two studies and reported with the following frequencies across subjects who received H5N1 A/turkey/Turkey/1/2005 irrespective of age or health status: diarrhoea (up to 11.9%), loss of appetite (up to 10.9%) and vomiting (up to 1.7%). In both studies, subjects with underlying medical and immunosuppressive conditions reported higher frequencies of diarrhoea, loss of appetite and vomiting compared to healthy subjects (irrespective of age).

Adverse reactions from clinical trial in children aged 6 months to 17 years

A clinical trial (Study V87P6) was conducted with a H5N1 A/Vietnam/1194/2004 vaccine combined with MF59C.1 adjuvant (N=334) vs seasonal influenza vaccine (N=137).

Regardless of age, reactogenicity was higher after the first dose than after the second vaccination. Reactogenicity after the third dose, administered 12 months following the second dose, was higher than after both first and second doses. The percentages of subjects reporting local adverse reactions were higher in the older age groups, mainly due to the higher reports for pain. In toddlers, erythema and tenderness were the most frequently reported solicited local adverse reactions; irritability and unusual crying were the most frequently reported solicited systemic adverse reactions. In children and adolescents, pain was the most frequently reported solicited local adverse reaction, and fatigue and headache were the most frequently reported solicited systemic adverse reactions. Across all ages, the frequency of fever after any dose was not more than 6%.

Study V87P6			
H5N1 MF59C.1 adjuvanted A/Vietnam/1194/2004 vaccine			
	First dose	Second dose (21 days after first dose)	Third dose (12 months after second dose)
Toddlers (6 to 35 months)	N=145	N=138	N=124
Any	76%	68%	80%
Local	47%	46%	60%
Systemic	59%	51%	54%
Fever $\geq 38^{\circ}\text{C}$ ($\geq 40^{\circ}\text{C}$)	0%	0%	0%
Any Other Adverse Event	54%	49%	35%
Children (3 to 8 years)	N=96	N=93	N=85
Any	72%	68%	79%
Local	66%	58%	74%
Systemic	32%	33%	45%
Fever $\geq 38^{\circ}\text{C}$ ($\geq 40^{\circ}\text{C}$)	4%	2%	6%
Any Other Adverse Event	36%	31%	19%
Adolescents(9 to 17 years)	N=93	N=91	N=83
Any	91%	82%	89%
Local	81%	70%	81%
Systemic	69%	52%	69%
Fever $\geq 38^{\circ}\text{C}$ ($\geq 40^{\circ}\text{C}$)	0%	1%	2%
Any Other Adverse Event	30%	27%	22%

Focetria (an MF59.1 adjuvanted H1N1 pandemic vaccine similar to Foclivia).

Adverse reactions in the week following vaccination with Focetria H1N1v from 77 children 3-8 years old and 80 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= 77	N= 75
Any adverse reaction	74%	69%
Local	62%	56%
Systemic	39%	35%
Fever $\geq 38^{\circ}\text{C}$ to 38.9°C	4%	1%
Fever 39°C to 39.9°C	0%	1%
Fever $\geq 40^{\circ}\text{C}$	0%	0%
Any other AE	14%	17%
Adolescents (9 to 17 years of age)	N= 80	N= 79
Any adverse reaction	79%	66%
Local	70%	58%
Systemic	45%	30%
Fever $\geq 38^{\circ}\text{C}$ to 38.9°C	3%	1%
Fever 39°C to 39.9°C	0%	0%
Fever $\geq 40^{\circ}\text{C}$	0%	0%
Any other AE	13%	10%

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 with Focetria H1N1v from 73 infants 6-11 months old and 73 toddlers 12-35 months old, receiving the 7.5 µg formulation were reported as follows:

	<i>Injection 1</i>	<i>Injection 2</i>
<i>Infants (6 to 11 months of age)</i>	<i>N= 73</i>	<i>N= 68</i>
<i>Any adverse reaction</i>	<i>79%</i>	<i>65%</i>
<i>Local</i>	<i>44%</i>	<i>26%</i>
<i>Systemic</i>	<i>70%</i>	<i>56%</i>
<i>Fever ≥ 38°C to 38.9°C</i>	<i>11%</i>	<i>9%</i>
<i>Fever 39°C to 39.9°C</i>	<i>3%</i>	<i>4%</i>
<i>Fever ≥ 40° C</i>	<i>0%</i>	<i>0%</i>
<i>Any other AE</i>	<i>32%</i>	<i>31%</i>
<i>Toddlers (12 to 35 months of age)</i>	<i>N= 73</i>	<i>N= 71</i>
<i>Any adverse reaction</i>	<i>70%</i>	<i>71%</i>
<i>Local</i>	<i>51%</i>	<i>49%</i>
<i>Systemic</i>	<i>60%</i>	<i>49%</i>
<i>Fever ≥ 38°C to 38.9°C</i>	<i>10%</i>	<i>11%</i>
<i>Fever 39°C to 39.9°C</i>	<i>4%</i>	<i>1%</i>
<i>Fever ≥ 40° C</i>	<i>1%</i>	<i>0%</i>
<i>Any other AE</i>	<i>21%</i>	<i>24%</i>

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 146 infants and toddlers 6 to 35 months of age:

Tenderness, erythema, irritability, unusual crying, sleepiness, diarrhoea, vomiting and change in eating habits. Induration and ecchymosis were very common reactions in toddlers but were less common in infants.

- Post-marketing surveillance

No post-marketing surveillance data are available following Foclivia administration.

The following adverse events were reported from post-marketing surveillance with Focetria (an H1N1 pandemic vaccine similar to Foclivia) which contains the same amount of adjuvant MF59C.1 as Foclivia, approved for use in children 6 months of age and above, adults and the elderly:

Blood and lymphatic system disorders

Lymphadenopathy.

Immune system disorders

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

Nervous system disorders

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

Cardiac disorders

Palpitation, tachycardia.

Respiratory disorders

Cough.

Gastrointestinal disorders

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

Skin and subcutaneous tissue disorders

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

Musculoskeletal, connective tissue and bone disorders

Muscular weakness, pain in extremities.

General disorders and administration site conditions

Asthenia.

The following additional adverse events were reported from post-marketing surveillance with seasonal non-adjuvanted trivalent vaccines in all age groups and a seasonal trivalent MF59-adjuvanted subunit influenza vaccine approved for use in elderly subjects 65 years of age and older:

Blood and lymphatic system disorders

Thrombocytopenia (in some cases reversible platelet counts less than 5000 mm³).

Nervous system disorders

Neurological disorders, such as encephalomyelitis and Guillain Barré syndrome.

Vascular disorders

Vasculitis which may be associated with transient renal involvement.

Skin and subcutaneous tissue disorders

Erythema multiforme.

General disorders and administration site conditions

Extensive swelling of injected limb lasting more than one week, injection-site cellulitis-like reaction (some cases of swelling, pain, and redness extending more than 10 cm and lasting more than 1 week).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccine, ATC Code: J07BB02

Clinical efficacy and safety

Pandemic preparedness 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 pandemic preparedness vaccine will support a vaccination strategy that is likely to be

used for the pandemic vaccine: clinical efficacy and safety data obtained with pandemic preparedness vaccines are relevant for the pandemic vaccines.

Immune response to H5N1 vaccine combined with MF59C.1 adjuvant containing A/Vietnam/1194/2004 or A/turkey/Turkey/1/2005 strain.

Adults (18-60 years)

A Phase II clinical trial (V87P1) was conducted with H5N1 MF59C.1 adjuvanted vaccine containing A/Vietnam/1194/2004 in 312 healthy adults. Two doses of vaccine containing 7.5 µg Haemagglutinin(HA)/dose were administered three weeks apart to 156 subjects. Immunogenicity was assessed in 149 subjects.

In a phase III clinical trial (V87P13), 2693 adult subjects were enrolled and 2566 received two doses of H5N1 MF59C.1 adjuvanted vaccine containing A/Vietnam/1194/2004 7.5 µg HA/dose administered three weeks apart. Immunogenicity was assessed in a subset (N=197) of subjects.

In a third clinical trial (V87P11) 194 adult subjects received two doses of H5N1 MF59C.1 adjuvanted vaccine containing A/turkey/Turkey/1/2005 7.5 µg HA/dose administered three weeks apart. Immunogenicity was assessed in 182 subjects.

The seroprotection rate*, seroconversion rate** and the seroconversion factor*** for anti-HA antibody to H5N1 A/Vietnam/1194/2004 and to H5N1 A/turkey/Turkey/1/2005 in the adults measured by Single Radial Haemolysis (SRH) assay was as follows:

Anti-HA antibody (SRH)	Study V87P1 A/Vietnam/1194/2004 21 days after 2 nd dose N=149	Study V87P13 A/Vietnam/1194/2004 21 days after 2 nd dose N=197	Study V87P11 A/turkey/Turkey/1/2005 21 days after 2 nd dose N=182
Seroprotection rate (95% CI)*	85% (79-91)	91% (87-95)	91% (85-94)
Seroconversion rate (95% CI)**	85% (78-90)	78% (72-84)	85% (79-90)
Seroconversion factor (95% CI)***	7.74 (6.6-9.07)	4.03 (3.54-4.59)	6 (5.2-6.93)

Anti-HA antibody (SRH)	Study V87P13 A/Vietnam/1194/2004 21 days after 2 nd dose N=69	Study V87P13 A/Vietnam/1194/2004 21 days after 2 nd dose N=128	-
Baseline Serostatus	< 4 mm ²	≥ 4 mm ²	-
Seroprotection rate (95% CI)*	87% (77-94)	94% (88-97)	-
Seroconversion rate (95% CI)**	87% (77-94)	73% (65-81)	-
Seroconversion factor (95% CI)***	8.87 (7.09-11)	2.71 (2.38-3.08)	-

* Seroprotection: SRH area ≥25 mm²

** Seroconversion was defined as an SRH area ≥25 mm² for subjects who were seronegative at baseline (Day 1 SRH area ≤4 mm²) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area >4 mm²)

*** geometric mean ratios (GMRs) of SRH

MicroNeutralization (MN) results against A/Vietnam/1194/2004 (Studies V87P1 and V87P13) indicate a seroprotection and seroconversion rate ranging from 67% (60-74) to 85% (78-90) and 65% (58-72) to 83% (77-89), respectively. Immune response to vaccination assessed by MN assay is in line with results obtained with SRH.

In Study V87P11 MN results against homologous A/turkey/Turkey/1/2005 indicate a seroprotection and seroconversion rate of 85% (79-90) and 93% (89-96), respectively. Immune response to vaccination assessed by MN assay is in line with results obtained with SRH.

Persistence of antibodies after primary vaccination in this population was assessed by Hemagglutination Inhibition (HI), SRH, and MN assays. Compared to the antibody levels obtained at day 43 after completion of primary vaccination schedules, antibody levels at day 202 were reduced by 1/5 to 1/2 from their prior levels.

Elderly (>61 years)

The seroprotection rate*, seroconversion rate** and the seroconversion factor*** for anti-HA antibody to H5N1 MF59C.1 adjuvanted vaccine (A/Vietnam/1194/2004 and A/turkey/Turkey/1/2005) in subjects aged 61 years and older (limited number of subjects were above 70 years of age; N=123) measured by SRH assay assessed in two clinical studies were as follows:

Anti-HA antibody (SRH)	Study V87P1 A/Vietnam/1194/2004 21 days after 2 nd dose N=84 ^a	Study V87P13 A/Vietnam/1194/2004 21 days after 2 nd dose N=210 ^b	Study V87P11 A/turkey/Turkey/1/2005 21 days after 2 nd dose N=132 ^c
Seroprotection rate (95% CI)*	80% (70-88)	82% (76-87)	82% (74-88)
Seroconversion rate (95% CI)**	70% (59-80)	63% (56-69)	70% (61-77)
Seroconversion factor (95% CI)***	4.96 (3.87-6.37)	2.9 (2.53-3.31)	3.97 (3.36-4.69)

Anti-HA antibody (SRH)	Study V87P13 A/Vietnam/1194/2004 21 days after 2 nd dose N=66	Study V87P13 A/Vietnam/1194/2004 21 days after 2 nd dose N=143
Baseline Serostatus	< 4 mm ²	≥ 4 mm ²
Seroprotection rate (95% CI)*	82% (70-90)	82% (75-88)
Seroconversion rate (95% CI)**	82% (70-90)	54% (45-62)
Seroconversion factor (95% CI)***	8.58 (6.57-11)	1.91 (1.72-2.12)

^a Ages 62-88 years; ^b Ages 61-68 years; ^c Ages 61-89 years

* Seroprotection: SRH area ≥25 mm²

** Seroconversion was defined as an SRH area ≥25 mm² for subjects who were seronegative at baseline (Day 1 SRH area ≤4 mm²) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area >4 mm²)

*** GMRs of SRH

MN results against A/Vietnam/1194/2004 (Studies V87P1 and V87P13) indicate a seroprotection and seroconversion rate ranging from 57% (50-64) to 79% (68-87) and 55% (48-62) to 58% (47-69) respectively. MN results, similar to SRH results, demonstrated strong immune response after completion of priming vaccination series in a population of elderly subjects.

In Study V87P11, MN results against homologous A/turkey/Turkey/1/2005 indicate a seroprotection and seroconversion rate of 68% (59-75) and 81% (74-87), respectively. Immune response to vaccination assessed by MN assay is similar to SRH results.

Persistence of antibodies after primary vaccination in this population as assessed by HI, SRH, and MN tests reduced from 1/2 to 1/5 of their post-vaccination level at day 202 as compared to day 43 after completion of primary schedules as assessed by HI, SRH, and MN tests. Up to 50% (N=33) of the elderly subjects aged 62 to 88 years immunised with H5N1 MF59C.1 adjuvanted vaccine containing A/Vietnam/1194/2004 in trial V87P1 were seroprotected at six months.

A third (booster) dose of H5N1 vaccine combined with MF59C.1 was administered 6 months after the primary vaccination series. Results are shown by SRH.

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

	Study V87P1 Adults A/Vietnam/1194/2004 booster after 2 nd dose	Study V87P2 Adults A/Vietnam/1194/2004 booster after 2 nd dose	Study V87P1 Elderly A/Vietnam/1194/2004 booster after 2 nd dose
SRH	N=71	N=13	N=38
Seroprotection rate (95% CI)*	89% (79-95)	85% (55-98)	84% (69-94)
Seroconversion rate (95% CI)**	83% (72-91)	69% (39-91)	63% (46-78)
Seroconversion factor (95% CI)***	5.96 (4.72-7.53)	2.49 (1.56-3.98)	5.15 (3.46-7.66)

* Seroprotection: SRH area ≥ 25 mm²

** Seroconversion was defined as an SRH area ≥ 25 mm² for subjects who were seronegative at baseline (Day 1 SRH area ≤ 4 mm²) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area > 4 mm²)

*** GMRs of SRH

- Supportive data in adult and elderly populations

In two dose finding studies 80 adults received an adjuvanted pandemic preparedness vaccine (H5N3 or H9N2). Two doses of vaccine with H5N3 (A/Duck/Singapore/97) strain at 3 different dosages (7.5, 15 and 30 μ g 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 μ g 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 μ g HA/dose), were administered four weeks apart. Serologic responses obtained with the HI assay showed that 92% of subjects achieved seroprotection and 75% seroconverted after two 7.5 μ g injections.

Cross reactivity

Cross-reactive immune response elicited by H5N1 A/Vietnam/1194/2004 against A/turkey/Turkey/1/2005 and A/Indonesia/5/2005

Adults (18-60 years)

Some heterologous immune response against A/turkey/Turkey/1/2005 (NIBRG23; clade 2.2.1) and A/Indonesia/5/2005 (clade 2.1) was detectable both after the second and third vaccinations, indicating cross-reactivity of the clade 1 vaccine against clade 2 strains.

Seroprotection rate*, seroconversion rate** and the seroconversion factor*** for anti-HA antibodies to H5N1 A/turkey/Turkey/1/2005 after the 2nd dose in adults 18-60 years of age, measured by SRH and HI assays were as follows:

	Anti-HA antibody	Study V87P1 A/Vietnam/1194/ 2004 21 days after 2 nd dose N=70	Study V87P12 A/Vietnam/1194/ 2004 21 days after 2 nd dose N=60	Study V87P3 A/Vietnam/1194/ 2004 21 days after 2 nd dose N=30	Study V87P13 A/Vietnam/1194/ 2004 21 days after 2 nd dose N=197
SRH	Seroprotection rate (95% CI)*	70% (58-80)	65% (52-77)	90% (73-98)	59% (52-66)
	Seroconversion rate (95% CI)**	NA†	65% (52-77)	86% (68-96)	49% (42-56)
	Seroconversion factor(95% CI)***	NA†	4.51 (3.63-5.61)	7.67 (6.09-9.67)	2.37 (2.1-2.67)
		N=69	N=60	N=30	N=197
HI	Seroprotection rate (95% CI) ^o	36% (25-49)	28% (17-41)	24% (10-44)	23% (18-30)
	Seroconversion rate (95% CI) ^o	NA†	28% (17-41)	21% (8-40)	19% (14-25)
	Seroconversion factor (95% CI) ^{oo}	NA†	2.3 (1.67-3.16)	1.98 (1.22-3.21)	1.92 (1.64-2.25)

* Seroprotection: SRH area ≥ 25 mm²

** Seroconversion was defined as an SRH area ≥ 25 mm² for subjects who were seronegative at baseline (Day 1 SRH area ≤ 4 mm²) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area > 4 mm²)

*** GMRs of SRH

† In V87P1: baseline not tested

^o measured by HI assay ≥ 40

^{oo} GMRs of HI

MN results for the clinical studies V87P12, V87P3 and V87P13 in the Table above revealed a seroprotection rate and seroconversion rate against A/turkey/Turkey/2005 ranging from 10% (2-27) to 39% (32-46) and 10% (2-27) to 36% (29-43) respectively. MN results yielded a GMR against A/turkey/Turkey/2005 ranging from 1.59 to 2.95.

Elderly (≥ 61 years)

Seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibodies to H5N1 A/turkey/Turkey/05 after the 2nd dose in elderly subjects ≥ 61 years of age, measured by SRH and HI assays were as follows:

	Anti-HA antibody	Study V87P1 A/Vietnam/1194/2004 21 days after 2 nd dose N=37	Study V87P13 A/Vietnam/1194/2004 21 days after 2 nd dose N=207
SRH	Seroprotection rate (95% CI)*	57% (39-73)	20% (18-23)
	Seroconversion rate (95% CI)*	NA***	48% (41-55)

	Seroconversion factor (95%CI)**	NA***	1.74 (1.57-1.94)
		N=36	N=208
HI	Seroprotection rate (95%CI) ^o	36% (21-54)	25% (19-32)
	Seroconversion rate (95%CI) ^o	NA***	19% (14-25)
	Seroconversion factor (95%CI) ^{oo}	NA***	1.79 (1.56-2.06)

* measured by SRH assay ≥ 25 mm²

** geometric mean ratios of SRH

^o measured by HI assay ≥ 40

^{oo} geometric mean ratios of HI

*** In V87P1: baseline not tested

MN results for the clinical studies in the Table above revealed a seroprotection rate against A/turkey/Turkey/05 ranging from 11% (3-25) (study V87P1) to 30% (24-37) (study V87P13) and seroconversion rate of 25% (19-31) for study V87P13. MN results in study V87P13 yielded a GMR against A/turkey/Turkey/05 of 2.01 (1.78-2.26).

Cross-reactive immune response elicited by A/turkey/Turkey/1/2005 against A/Indonesia/5/2005 and A/Vietnam/1194/2004

Heterologous immune response against A/Indonesia/5/2005 (clade 2.1) was detectable in Study V87P11 after the second vaccination, indicating cross-reactivity of the clade 2.2.1 vaccine against clade 2.1 strains.

Seroprotection rate*, seroconversion rate** and the seroconversion factor*** for anti-HA antibodies to H5N1 A/Indonesia/5/2005 and A/Vietnam/1194/2004 after the 2nd dose in adults (18-60 years) and elderly (≥ 61 years), measured by SRH and HI assays were as follows:

Anti-HA antibody		V87P11 Adults (18-60 years) N=186		V87P11 Elderly (≥ 61 -89 years) ^a N=142	
		A/Indonesia/ 5/2005	A/Vietnam/ 1194/2004	A/Indonesia/ 5/2005	A/Vietnam/ 1194/2004
SRH	Seroprotection rate (95%CI)*	83 (77-88)	62 (54-69)	61 (52-69)	45 (37-54)
	Seroconversion rate (95%CI)**	79 (72-85)	60 (53-68)	64 (56-73)	44 (35-53)
	Seroconversion factor (95%CI)***	6.24 (5.44-7.16)	4.45 (3.85-5.14)	3.87 (3.31-4.53)	3.03 (2.56-3.58)
		N=194		N=148	
HI	Seroprotection rate (95%CI) ^o	50 (43-57)	47 (40-55)	34 (26-42)	39 (31-48)
	Seroconversion rate (95%CI) ^o	49 (42-56)	44 (37-51)	32 (25-41)	34 (26-42)
	Seroconversion factor (95%CI) ^{oo}	4.71 (3.74-5.93)	4.25 (3.36-5.37)	2.69 (2.18-3.32)	2.8 (2.2-3.55)

^a actual age range of population enrolled

* Seroprotection: SRH area ≥ 25 mm²

** Seroconversion was defined as an SRH area ≥ 25 mm² for subjects who were seronegative at baseline (Day 1 SRH area ≤ 4 mm²) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area > 4 mm²)

*** GMRs of SRH

^o measured by HI assay ≥ 40

^{oo} GMRs of HI

MN results for A/Indonesia/5/2005 revealed a seroprotection rate of 38% (31-45) in adults (18-60 years) and 14% (8-20) in elderly (≥ 61 years); a seroconversion rate of 58% (50-65) in adults and 30% (23-38) in elderly and finally a GMR of 4.67 (3.95-5.56) in adults and 2.19 (1.86-2.58) in elderly.

MN results for A/Vietnam/1194/2004 revealed a seroprotection rate of 10% (6-16) in adults (18-60 years) and 6% (3-11) in elderly (≥ 61 years); a seroconversion rate of 19% (13-25) in adults and 7% (4-13) in elderly and finally a GMR of 1.86 (1.63-2.12) in adults and 1.33 (1.17-1.51) in elderly.

Long term booster immune memory:

A single vaccination with H5N1 MF59C.1 adjuvanted A/Vietnam/1194/2004 vaccine induced high and rapid serological response in subjects primed 6-8 years previously with two doses of a different vaccine, having the same formulation but using the H5N3 strain.

In a phase I clinical trial (V87P3) adult subjects aged 18-65 years primed 6-8 years previously with 2 doses of MF59-adjuvanted H5N3 vaccine/A/Duck/Singapore/97, were administered 2 booster doses of H5N1 MF59C.1 adjuvanted A/Vietnam/1194/2004 vaccine. SRH results after the first dose, that mimic pre-pandemic priming plus single heterologous booster dose, revealed seroprotection and seroconversion rates of 100% (74- 100) and an 18-fold increase in SRH area (GMR).

Alternative vaccination schedules:

In a clinical trial evaluating 4 different vaccination schedules in 240 subjects 18 to 60 years of age, where the second dose occurred either 1, 2, 3 or 6 weeks after the first dose of H5N1 MF59C.1 adjuvanted A/Vietnam/1194/2004 vaccine, all vaccine schedule groups after 3 weeks from the 2nd vaccination achieved high levels of antibodies as evaluated with SRH. SRH seroprotection rates ranged from 86% to 98%, seroconversion rates from 64% to 90%, and GMR ranged from 2.92 to 4.57. The magnitude of immune response was lower in the group who received the 2nd dose 1 week later and higher in the groups with longer interval schedules.

Subjects with underlying medical or immunosuppressive conditions:

Immunogenicity of H5N1 A/turkey/Turkey/1/2005 in adults (18 to 60 years) and elderly (≥ 61 years) subjects with underlying medical conditions (Study V87_25) or immunosuppressive conditions (mainly HIV-infected subjects) (Study V87_26) in comparison to healthy adults (18-60 years) and elderly (≥ 61 years), was evaluated in two randomised, phase III controlled clinical trials (with a seasonal trivalent inactivated MF59-adjuvanted subunit influenza vaccine approved for use in elderly subjects 65 years of age and older as a comparator). In trial V87_25 and V87_26, 96 and 67 subjects, respectively, were over the age of 70 years. In both trials, immunogenicity of H5N1 A/turkey/Turkey/1/2005 was shown by HI, SRH and MN assays following both the first and second dose.

Geometric mean area*, seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibody to H5N1 A/turkey/Turkey/1/2005 measured by SRH assays 21 days after the 2nd dose were as follows:

Study V87_25				
	Adults (20- 60 years) ^a	Adults (19- 60 years) ^a	Elderly (61-84 years) ^a	Elderly (61-79 years) ^a
Anti-HA antibody (SRH)	Medical Conditions N=140	Healthy N=57	Medical Conditions N=143	Healthy N=57
Geometric Mean Area (95%CI)*	31.07 (27.43-35.19)	58.02 (48.74-69.06)	29.34 (26.07-33.01)	27.78 (22.57-34.18)
Seroprotection rate (95%CI)*	65.00 (56.5-72.9)	89.47 (78.5-96)	58.74 (50.2-66.9)	57.89 (44.1-70.9)
Seroconversion rate (95%CI)*	72.86 (64.7-80)	98.25 (90.6-99.96)	64.34 (55.9-72.2)	66.67 (52.9-78.6)

Seroconversion factor (95% CI)**	3.33 (2.94-3.77)	6.58 (5.53-7.83)	2.37 (2.10-2.66)	2.96 (2.41-3.64)
Study V87_26				
	Adults (20- 60 years) ^a	Adults (18-59 years) ^a	Elderly (61-84 years) ^a	Elderly (61-91 years) ^a
Anti-HA antibody (SRH)	Immuno-compromised N=143	Healthy N=57	Immuno-compromised N=139	Healthy N=62
Geometric Mean Area (95% CI)*	26.50 (22.49-31.22)	48.58 (40.01-58.99)	26.85 (23.01-31.33)	23.91 (18.89-30.26)
Seroprotection rate (95% CI)*	60.84 (52.3-68.9)	87.72 (76.3-94.9)	58.99 (50.3-67.3)	53.23 (40.1-66)
Seroconversion rate (95% CI)*	61.54 (53-69.5)	89.47 (78.5-96)	64.75 (56.2-72.7)	56.45 (43.3-69)
Seroconversion factor (95% CI)**	3.16 (2.69-3.73)	7.10 (5.85-8.62)	3.15 (2.70-3.68)	2.83 (2.24-3.58)

^a actual age range of population enrolled

* measured by SRH assay seroprotection: SRH area ≥ 25 mm², seroconversion: SRH area ≥ 25 mm² for subjects with a baseline SRH area ≤ 4 mm² or a minimum 50% increase in SRH area for subjects with >4 mm².

** geometric mean ratios of SRH

HI results for the two clinical studies revealed lower values than those reported in previous studies. Seroconversion rates against homologous A/turkey/Turkey/1/2005 ranged from 37.50% to 43.10% in healthy adults, and from 19.18% to 26.47% in adults with immunosuppressive or underlying medical conditions, respectively; seroconversion rates ranged from 21.43% to 30.65% in healthy elderly subjects, and from 24.49% to 27.86% in elderly subjects with immunosuppressive or underlying medical conditions. Similar trends were observed for seroprotection rates in both studies.

MN results against homologous A/turkey/Turkey/1/2005 indicate a seroconversion rate of 66.67% in healthy adults, and ranging from 33.57% to 54.14% in adults with immunosuppressive or underlying medical conditions, respectively; seroconversion rates ranged from 24.39% to 29.03% in healthy elderly subjects, and from 31.65% to 39.42% in elderly subjects with immunosuppressive or underlying medical conditions. Similar trends were observed for seroprotection rates in both studies.

In both studies V87_25 and V87_26, the lower levels of antibodies (as measured by HI, SRH and MN assays) and reduced seroprotection rates in adults and elderly (≥ 61 years old) subjects with underlying medical or immunosuppressive conditions, suggest that H5N1 A/turkey/Turkey/1/2005 may not elicit the same level of protection against A/H5N1 strain as compared to healthy adults (see section 4.4). These studies provided limited immunogenicity data in subjects with some underlying medical (in particular, renal impairment and peripheral cardiovascular disease) and immunosuppressive conditions (in particular, transplant recipients and patients under cancer treatment). In these trials, lower levels of antibodies and reduced seroprotection rates against homologous H5N1 A/turkey/Turkey/1/2005 were also measured in healthy elderly subjects, as compared to healthy adults, though previous studies showed induction of sufficiently immunogenic responses against H5N1 strains (see above for information on elderly).

Available data in paediatric populations

A clinical trial (V87P6) was conducted with a H5N1 A/Vietnam/1194/2004 vaccine combined with MF59C.1 adjuvant in 471 children from 6 months to 17 years of age. Two doses of 7.5 μ g were administered three weeks apart and a third dose 12 months following the first dose. After 3 weeks from the 2nd vaccination (day 43) all age groups (i.e. 6-35 months, 3-8 years and 9-17 years) achieved high levels of antibodies to A/Vietnam/1194/2004 as evaluated with SRH and HI assays as presented in table below. In this trial no vaccine related SAEs were observed.

		Toddlers (6 to 35 months)	Children (3 to 8 years)	Adolescents (9 to 17 years)
		N=134	N=91	N=89
HI	Seroprotection rate (95% CI) Day 43	97% (92-99)	97% (91-99)	89% (80-94)
	Seroconversion factor (95% CI) Day 43 to Day 1	129 (109-151)	117 (97-142)	67 (51-88)
	Seroconversion rate (95% CI) Day 43	97% (92-99)	97% (91-99)	89% (80-94)
SRH		N=133	N=91	N=90
	Seroprotection rate (95% CI) Day 43	100% (97-100)	100% (96-100)	100% (96-100)
	Seroconversion factor (95% CI) Day 43 to Day 1	16 (14-18)	15 (13-17)	14 (12-16)
	Seroconversion rate (95% CI) Day 43	98% (95-100)	100% (96-100)	99% (94-100)

MN results against a A/Vietnam/1194/2004 indicate a seroprotection rate of 99% (95%CI: 94-100), a seroconversion rate ranging from 97% (95%CI: 91-99) to 99% (95%CI: 96-100) and a GMR ranging from 29 (95%CI: 25-35) to 50 (95%CI: 44-58).

Immunogenicity results with Focetria H1N1v (Study V111_03):

The seroprotection rate and seroconversion rate measured by HI assay and the seroconversion factor expressed as geometric mean ratio of HI for anti-HA antibody to H1N1 after administration of one and two 7.5 µg doses of Focetria was evaluated in 70 children and adolescents (9-17 years), 60 children (3-8 years), 58 children (12-35 months) and 49 infants (6-11 months). CHMP immunogenicity criteria set for adults (18-60 years) were met both after the 1st and the 2nd dose in all the above age strata (both in the overall population and in the subset seronegative at baseline).

The European medicines Agency has deferred the obligation to submit the results of studies with Foclivia in one or more subsets of the paediatric populations in active immunisation against H5N1 subtype of Influenza A virus. See section 4.2 for information on paediatric use.

Foclivia has been authorised under “Exceptional Circumstances”.

This means that for scientific reasons, it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency (EMA) will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data obtained with Foclivia and with seasonal influenza vaccine containing MF59C.1 adjuvant reveal no special hazard for humans based on conventional studies of repeated dose toxicity, local tolerance, female fertility, and reproductive and developmental toxicity (through the end of the lactation period).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride,
Potassium chloride,
Potassium dihydrogen phosphate,
Disodium phosphate dihydrate,
Magnesium chloride hexahydrate,
Calcium chloride dihydrate,

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. Discard if the vaccine has been frozen. 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 with or without needle. Syringes without needle are fitted with a Luer Lock system.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Gently shake before use.

After shaking, the normal appearance of Foclivia is a milky-white suspension.

Visually inspect the suspension prior to administration. In case of any particles and/or abnormal appearance, the vaccine should be discarded.

When using a pre-filled syringe without needle supplied with a Luer Lock system, remove the tip cap by unscrewing it in a counter-clockwise direction. Once the tip cap is removed, attach a needle to the syringe by screwing it on in a clockwise direction until it locks. Once the needle is locked in place, remove the needle protector and administer the vaccine.

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

7. MARKETING AUTHORISATION HOLDER

Seqirus S.r.l.
Via del Pozzo 3/A, S. Martino
53035 Monteriggioni (SI)

Italy

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/577/001-002

EU/1/09/577/005-006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 October 2009

Date of latest renewal: 19 October 2014

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Foclivia suspension for injection

Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

A/Vietnam/1194/2004 (H5N1) 7.5 micrograms**
per 0.5 ml dose

* propagated in fertilised hens' eggs from healthy chicken flocks

** expressed in microgram haemagglutinin.

Adjuvant MF59C.1 containing:

Squalene	9.75 milligrams
Polysorbate 80	1.175 milligrams
Sorbitan trioleate	1.175 milligrams
Sodium citrate	0.66 milligrams
Citric acid	0.04 milligrams

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

Excipient with known effect:

The vaccine contains 1.899 milligrams of sodium and 0.081 milligrams of potassium per 0.5 ml dose.

Foclivia may contain trace residues of egg and chicken proteins, ovalbumin, kanamycin sulphate, neomycin sulphate, formaldehyde and cetyltrimethylammonium bromide which are used during the manufacturing process (see section 4.3).

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 in an officially declared pandemic situation.

Foclivia should be used in accordance with Official Guidance.

4.2 Posology and method of administration

Posology

Adults and elderly (18 years of age and above): 0.5 ml at an elected date.

A second dose of vaccine should be given after an interval of at least 3 weeks.

Foclivia was evaluated in adults (aged 18 to 60 years old) and elderly (over 60 years old) following a 1, 22 day primary vaccination schedule.

Data on a third dose (booster) administered 6 months after the first dose are limited (see sections 4.8 and 5.1).

Paediatric population

The safety and efficacy of Foclivia in subjects under 18 years of age have not yet been established. Currently available data in subjects aged 6 months to 18 years of age are described in section 5.1 but no recommendation on a posology can be made.

No data are available in children aged less than 6 months.

Method of administration

Immunisation should be carried out by intramuscular injection 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 (eggs, chicken proteins, ovalbumin, kanamycin sulphate, neomycin sulphate, formaldehyde and cetyltrimethylammonium bromide) of this vaccine. However, in a pandemic situation, it may be appropriate to give this vaccine to individuals with a history of anaphylaxis as defined above, provided that facilities for resuscitation are immediately available in case of need. See section 4.4.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Caution is needed when administering this vaccine to persons with a known hypersensitivity to the active substance, to any of the excipients listed in section 6.1 and to residues (eggs, chicken proteins, ovalbumin, kanamycin sulphate, neomycin sulphate, formaldehyde and cetyltrimethylammonium bromide).

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

If the pandemic situation allows, immunisation should be postponed in patients with febrile illness until the fever is resolved.

The vaccine should under no circumstances be administered intravascularly or intradermally. There are no data with Foclivia using the subcutaneous route of administration. 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 bleeding.

Protection against influenza

There is no immune correlate of protection established for influenza A (H5N1).

A protective immune response may not be elicited in all vaccine recipients. In addition, antibody responses in patients with endogenous or iatrogenic immunosuppression may be insufficient to provide protection.

Some degree of cross-reactive immunity has been observed against H5N1 viruses of clades different to that of the vaccine strain. However, the degree of protection that may be elicited to H5N1 strains of other clades is unknown (see section 5.1).

Since a second dose is recommended, it should be noted that there are no safety, immunogenicity or efficacy data to support interchangeability of Foclivia with other H5N1 monovalent vaccines.

While no data are available from the use of Foclivia, cases of convulsion with and without fever have been reported in subjects vaccinated with Focetria, an MF59.1 adjuvanted H1N1 pandemic vaccine similar to Foclivia.

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).

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

4.5 Interaction with other medicinal products and other forms of interaction

Foclivia may be co-administered with non-adjuvanted seasonal influenza vaccines, and immunisation should be carried out on separate limbs.

There are no data on co-administration of Foclivia with vaccines other than non-adjuvanted seasonal influenza 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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Limited data obtained from women who became pregnant during the course of clinical trials with Foclivia or other pandemic vaccines adjuvanted with MF59C.1 were insufficient to inform vaccine-associated risks in pregnancy.

However, it is estimated that during the 2009 H1N1 pandemic more than 90,000 women were vaccinated during pregnancy with Focetria (an H1N1 pandemic vaccine similar to Foclivia) which contains the same amount of MF59C.1 as Foclivia. Post-marketing spontaneously reported adverse events and an interventional study do not suggest direct or indirect harmful effects of Focetria exposure on pregnancy. In addition, two large observational studies designed to assess the safety of Focetria exposure in pregnancy showed no increase in the rates of gestational diabetes, preeclampsia, abortions, stillbirth, low birth weight, prematurity, neonatal deaths, and congenital malformations among almost 10,000 vaccinated pregnant women and their offspring compared with unvaccinated controls.

Health care providers need to assess the benefits and potential risks of administering Foclivia vaccine to pregnant women, taking into consideration official recommendations.

Breast-feeding

There are no data regarding the use of Foclivia during breast-feeding. The potential benefits and risks to the mother and infant should be considered before administering Foclivia.

Fertility

There are no data concerning human fertility. A study in female rabbits did not indicate reproductive or developmental toxicity of Foclivia. Male fertility has not been assessed in animals (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

- Clinical trials

Adverse reactions from clinical trial in adults and elderly (above 18 years old)

The incidence of adverse reactions has been evaluated in seven clinical trials in healthy subjects involving over 4300 adults and elderly receiving H5N1 vaccine combined with MF59C.1 adjuvant (at least 7.5 µg haemagglutinin, HA) containing either the A/turkey/Turkey/1/2005 or the A/Vietnam/1194/2004 strain. There were 3872 subjects 18-60 years of age, 365 subjects 61-70 years of age, and 89 subjects greater than 70 years of age. The safety profile across clinical trials using H5N1 vaccine containing either the A/turkey/Turkey/1/2005 or the A/Vietnam/1194/2004 strain is comparable (see section 5.1). Clinical trials in 80 subjects receiving adjuvanted vaccine with an H5N3 or an H9N2 strain showed a similar safety profile.

Across all trials, there was a general trend towards decreased reports of solicited local adverse reactions after the second vaccination compared with the first.

Irrespective of antigen dose, almost all solicited systemic adverse reactions were reported on the day of vaccination (day 1) or during the 3 days immediately following.

Data on safety of a booster dose are limited to three trials performed with H5N1 MF59C.1 adjuvanted vaccine containing A/Vietnam/1194/2004 (V87P1, V87P2) or A/turkey/Turkey/1/2005 (V87P1E1) that included 116 adults (18-60 years) and 56 elderly subjects (≥61 years). No increase in solicited adverse reactions was reported when a booster dose was administered 6 or 18 months, after the initial dosing series. A slight increase in solicited adverse reactions in adults was reported when a booster dose was administered 18 months after the initial dosing series. In the elderly, the reported solicited adverse reactions increased with the third booster dose only when compared with the second dose.

Tabulated list of adverse reactions

The adverse reaction rates reported after any vaccination dose (i.e. 1st, 2nd or booster) were similar and are listed according to the following MedDRA frequency convention and system organ class: 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).

MedDRA System Organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Rare (≥1/10,000 to <1/1,000)
Nervous system disorders	Headache		
Gastrointestinal disorders		Nausea	
Skin and subcutaneous tissue disorders		Sweating	

Musculoskeletal and connective tissue disorders	Myalgia	Arthralgia	
General disorders and administration site conditions	Injection site swelling, Injection site pain, Injection site induration, Injection site redness, Fatigue, Chills, Malaise	Injection site ecchymosis, Fever	Anaphylaxis

The majority of these reactions usually disappear within 1-2 days without treatment.

Clinical trials in special populations

Adverse reactions in special populations have been evaluated in two clinical trials, V87_25 and V87_26, involving adult (18-60 years) and elderly (≥ 61 years) subjects who were either healthy or with underlying medical conditions or immunosuppressive conditions.

H5N1 MF59C.1 adjuvanted A/turkey/Turkey/1/2005 vaccine								
Study V87_25					Study V87_26			
	Medical conditions		Healthy		Immunocompromised		Healthy	
	Adults (20-60 years)*	Elderly (61-84 years)*	Adults (19-60 years)*	Elderly (61-79 years)*	Adults (20-60 years)*	Elderly (61-84 years)*	Adults (18-59 years)*	Elderly (61-91 years)*
No. of subjects	N=145	N=149	N=59	N=58	N=147	N=148	N=58	N=62

*actual age range of population enrolled

Across studies V87_25 and V87_26, the safety of H5N1 A/turkey/Turkey/1/2005 in healthy adult and elderly subjects was consistent with existing safety data from previous clinical trials. However, in immunocompromised subjects 18 through 60 years of age, slightly higher rates of nausea (13.0%) were reported. In addition, higher rates of arthralgia (up to 23.3%) were reported in both adult and elderly subjects, who were immunocompromised or with underlying medical conditions.

The following solicited adverse reactions were additionally collected in these two studies and reported with the following frequencies across subjects who received H5N1 A/turkey/Turkey/1/2005 irrespective of age or health status: diarrhoea (up to 11.9%), loss of appetite (up to 10.9%) and vomiting (up to 1.7%). In both studies, subjects with underlying medical and immunosuppressive conditions reported higher frequencies of diarrhoea, loss of appetite and vomiting compared to healthy subjects (irrespective of age).

Adverse reactions from clinical trial in children aged 6 months to 17 years

A clinical trial (Study V87P6) was conducted with a H5N1 A/Vietnam/1194/2004 vaccine combined with MF59C.1 adjuvant (N=334) vs seasonal influenza vaccine (N=137).

Regardless of age, reactogenicity was higher after the first dose than after the second vaccination. Reactogenicity after the third dose, administered 12 months following the second dose, was higher than after both first and second doses. The percentages of subjects reporting local adverse reactions were higher in the older age groups, mainly due to the higher reports for pain. In toddlers, erythema and tenderness were the most frequently reported solicited local adverse reactions; irritability and unusual crying were the most frequently reported solicited systemic adverse reactions. In children and adolescents, pain was the most frequently reported solicited local adverse reaction, and fatigue and headache were the most frequently reported solicited systemic adverse reactions. Across all ages, the frequency of fever after any dose was not more than 6%.

Study V87P6			
H5N1 MF59C.1 adjuvanted A/Vietnam/1194/2004 vaccine			
	First dose	Second dose (21 days after first dose)	Third dose (12 months after second dose)
Toddlers (6 to 35 months)	N=145	N=138	N=124
Any	76%	68%	80%
Local	47%	46%	60%
Systemic	59%	51%	54%
Fever $\geq 38^{\circ}\text{C}$ ($\geq 40^{\circ}\text{C}$)	0%	0%	0%
Any Other Adverse Event	54%	49%	35%
Children (3 to 8 years)	N=96	N=93	N=85
Any	72%	68%	79%
Local	66%	58%	74%
Systemic	32%	33%	45%
Fever $\geq 38^{\circ}\text{C}$ ($\geq 40^{\circ}\text{C}$)	4%	2%	6%
Any Other Adverse Event	36%	31%	19%
Adolescents(9 to 17 years)	N=93	N=91	N=83
Any	91%	82%	89%
Local	81%	70%	81%
Systemic	69%	52%	69%
Fever $\geq 38^{\circ}\text{C}$ ($\geq 40^{\circ}\text{C}$)	0%	1%	2%
Any Other Adverse Event	30%	27%	22%

Focetria (an MF59.1 adjuvanted H1N1 pandemic vaccine similar to Foclivia).

Adverse reactions in the week following vaccination with Focetria H1N1v from 77 children 3-8 years old and 80 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= 77	N= 75
Any adverse reaction	74%	69%
Local	62%	56%
Systemic	39%	35%
Fever $\geq 38^{\circ}\text{C}$ to 38.9°C	4%	1%
Fever 39°C to 39.9°C	0%	1%
Fever $\geq 40^{\circ}\text{C}$	0%	0%
Any other AE	14%	17%
Adolescents (9 to 17 years of age)	N= 80	N= 79
Any adverse reaction	79%	66%
Local	70%	58%
Systemic	45%	30%
Fever $\geq 38^{\circ}\text{C}$ to 38.9°C	3%	1%
Fever 39°C to 39.9°C	0%	0%
Fever $\geq 40^{\circ}\text{C}$	0%	0%
Any other AE	13%	10%

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 with Focetria H1N1v from 73 infants 6-11 months old and 73 toddlers 12-35 months old, receiving the 7.5 µg formulation were reported as follows:

	<i>Injection 1</i>	<i>Injection 2</i>
<i>Infants (6 to 11 months of age)</i>	<i>N= 73</i>	<i>N= 68</i>
<i>Any adverse reaction</i>	79%	65%
<i>Local</i>	44%	26%
<i>Systemic</i>	70%	56%
<i>Fever ≥ 38°C to 38.9°C</i>	11%	9%
<i>Fever 39°C to 39.9°C</i>	3%	4%
<i>Fever ≥ 40° C</i>	0%	0%
<i>Any other AE</i>	32%	31%
<i>Toddlers (12 to 35 months of age)</i>	<i>N= 73</i>	<i>N= 71</i>
<i>Any adverse reaction</i>	70%	71%
<i>Local</i>	51%	49%
<i>Systemic</i>	60%	49%
<i>Fever ≥ 38°C to 38.9°C</i>	10%	11%
<i>Fever 39°C to 39.9°C</i>	4%	1%
<i>Fever ≥ 40° C</i>	1%	0%
<i>Any other AE</i>	21%	24%

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 146 infants and toddlers 6 to 35 months of age: Tenderness, erythema, irritability, unusual crying, sleepiness, diarrhoea, vomiting and change in eating habits. Induration and ecchymosis were very common reactions in toddlers but were less common in infants.

- Post-marketing surveillance

No post-marketing surveillance data are available following Foclivia administration.

The following adverse events were reported from post-marketing surveillance with Focetria (an H1N1 pandemic vaccine similar to Foclivia) which contains the same amount of adjuvant MF59C.1 as Foclivia, approved for use in children 6 months of age and above, adults and the elderly:

Blood and lymphatic system disorders

Lymphadenopathy.

Immune system disorders

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

Nervous system disorders

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

Cardiac disorders

Palpitation, tachycardia.

Respiratory disorders

Cough.

Gastrointestinal disorders

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

Skin and subcutaneous tissue disorders

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

Musculoskeletal, connective tissue and bone disorders

Muscular weakness, pain in extremities.

General disorders and administration site conditions

Asthenia.

The following additional adverse events were reported from post-marketing surveillance with seasonal non-adjuvanted trivalent vaccines in all age groups and a seasonal trivalent MF59-adjuvanted subunit influenza vaccine approved for use in elderly subjects 65 years of age and older:

Blood and lymphatic system disorders

Thrombocytopenia (in some cases reversible platelet counts less than 5000 mm³).

Nervous system disorders

Neurological disorders, such as encephalomyelitis and Guillain Barré syndrome.

Vascular disorders

Vasculitis which may be associated with transient renal involvement.

Skin and subcutaneous tissue disorders

Erythema multiforme.

General disorders and administration site conditions

Extensive swelling of injected limb lasting more than one week, injection-site cellulitis-like reaction (some cases of swelling, pain, and redness extending more than 10 cm and lasting more than 1 week).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#)

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccine, ATC Code: J07BB02

Clinical efficacy and safety

Pandemic preparedness 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 pandemic preparedness vaccine will support a vaccination strategy that is likely to be

used for the pandemic vaccine: clinical efficacy and safety data obtained with pandemic preparedness vaccines are relevant for the pandemic vaccines.

Immune response to H5N1 vaccine combined with MF59C.1 adjuvant containing A/Vietnam/1194/2004 or A/turkey/Turkey/1/2005 strain.

Adults (18-60 years)

A Phase II clinical trial (V87P1) was conducted with H5N1 MF59C.1 adjuvanted vaccine containing A/Vietnam/1194/2004 in 312 healthy adults. Two doses of vaccine containing 7.5 µg Haemagglutinin(HA)/dose were administered three weeks apart to 156 subjects. Immunogenicity was assessed in 149 subjects.

In a phase III clinical trial (V87P13), 2693 adult subjects were enrolled and 2566 received two doses of H5N1 MF59C.1 adjuvanted vaccine containing A/Vietnam/1194/2004 7.5 µg HA/dose administered three weeks apart. Immunogenicity was assessed in a subset (N=197) of subjects.

In a third clinical trial (V87P11) 194 adult subjects received two doses of H5N1 MF59C.1 adjuvanted vaccine containing A/turkey/Turkey/1/2005 7.5 µg HA/dose administered three weeks apart. Immunogenicity was assessed in 182 subjects.

The seroprotection rate*, seroconversion rate** and the seroconversion factor*** for anti-HA antibody to H5N1 A/Vietnam/1194/2004 and to H5N1 A/turkey/Turkey/1/2005 in the adults measured by Single Radial Haemolysis (SRH) assay was as follows:

Anti-HA antibody (SRH)	Study V87P1 A/Vietnam/1194/2004 21 days after 2 nd dose N=149	Study V87P13 A/Vietnam/1194/2004 21 days after 2 nd dose N=197	Study V87P11 A/turkey/Turkey/1/2005 21 days after 2 nd dose N=182
Seroprotection rate (95%CI)*	85% (79-91)	91% (87-95)	91% (85-94)
Seroconversion rate (95%CI)**	85% (78-90)	78% (72-84)	85% (79-90)
Seroconversion factor (95%CI)***	7.74 (6.6-9.07)	4.03 (3.54-4.59)	6 (5.2-6.93)

Anti-HA antibody (SRH)	Study V87P13 A/Vietnam/1194/2004 21 days after 2 nd dose N=69	Study V87P13 A/Vietnam/1194/2004 21 days after 2 nd dose N=128	-
Baseline Serostatus	< 4 mm ²	≥ 4 mm ²	-
Seroprotection rate (95%CI)*	87% (77-94)	94% (88-97)	-
Seroconversion rate (95%CI)**	87% (77-94)	73% (65-81)	-
Seroconversion factor (95%CI)***	8.87 (7.09-11)	2.71 (2.38-3.08)	-

* Seroprotection: SRH area ≥25 mm²

** Seroconversion was defined as an SRH area ≥25 mm² for subjects who were seronegative at baseline (Day 1 SRH area ≤4 mm²) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area >4 mm²)

*** geometric mean ratios (GMRs) of SRH

MicroNeutralization (MN) results against A/Vietnam/1194/2004 (Studies V87P1 and V87P13) indicate a seroprotection and seroconversion rate ranging from 67% (60-74) to 85% (78-90) and 65% (58-72) to 83% (77-89), respectively. Immune response to vaccination assessed by MN assay is in line with results obtained with SRH.

In Study V87P11 MN results against homologous A/turkey/Turkey/1/2005 indicate a seroprotection and seroconversion rate of 85% (79-90) and 93% (89-96), respectively. Immune response to vaccination assessed by MN assay is in line with results obtained with SRH.

Persistence of antibodies after primary vaccination in this population was assessed by Hemagglutination Inhibition (HI), SRH, and MN assays. Compared to the antibody levels obtained at day 43 after completion of primary vaccination schedules, antibody levels at day 202 were reduced by 1/5 to 1/2 from their prior levels.

Elderly (>61 years)

The seroprotection rate*, seroconversion rate** and the seroconversion factor*** for anti-HA antibody to H5N1 MF59C.1 adjuvanted vaccine (A/Vietnam/1194/2004 and A/turkey/Turkey/1/2005) in subjects aged 61 years and older (limited number of subjects were above 70 years of age; N=123) measured by SRH assay assessed in two clinical studies were as follows:

Anti-HA antibody (SRH)	Study V87P1 A/Vietnam/1194/2004 21 days after 2 nd dose N=84 ^a	Study V87P13 A/Vietnam/1194/2004 21 days after 2 nd dose N=210 ^b	Study V87P11 A/turkey/Turkey/1/2005 21 days after 2 nd dose N=132 ^c
Seroprotection rate (95% CI)*	80% (70-88)	82% (76-87)	82% (74-88)
Seroconversion rate (95% CI)**	70% (59-80)	63% (56-69)	70% (61-77)
Seroconversion factor (95% CI)***	4.96 (3.87-6.37)	2.9 (2.53-3.31)	3.97 (3.36-4.69)

Anti-HA antibody (SRH)	Study V87P13 A/Vietnam/1194/2004 21 days after 2 nd dose N=66	Study V87P13 A/Vietnam/1194/2004 21 days after 2 nd dose N=143
Baseline Serostatus	< 4 mm ²	≥ 4 mm ²
Seroprotection rate (95% CI)*	82% (70-90)	82% (75-88)
Seroconversion rate (95% CI)**	82% (70-90)	54% (45-62)
Seroconversion factor (95% CI)***	8.58 (6.57-11)	1.91 (1.72-2.12)

^a Ages 62-88 years; ^b Ages 61-68 years; ^c Ages 61-89 years

* Seroprotection: SRH area ≥25 mm²

** Seroconversion was defined as an SRH area ≥25 mm² for subjects who were seronegative at baseline (Day 1 SRH area ≤4 mm²) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area >4 mm²)

*** GMRs of SRH

MN results against A/Vietnam/1194/2004 (Studies V87P1 and V87P13) indicate a seroprotection and seroconversion rate ranging from 57% (50-64) to 79% (68-87) and 55% (48-62) to 58% (47-69) respectively. MN results, similar to SRH results, demonstrated strong immune response after completion of priming vaccination series in a population of elderly subjects.

In Study V87P11, MN results against homologous A/turkey/Turkey/1/2005 indicate a seroprotection and seroconversion rate of 68% (59-75) and 81% (74-87), respectively. Immune response to vaccination assessed by MN assay is similar to SRH results.

Persistence of antibodies after primary vaccination in this population as assessed by HI, SRH, and MN tests reduced from 1/2 to 1/5 of their post-vaccination level at day 202 as compared to day 43 after

completion of primary schedules as assessed by HI, SRH, and MN tests. Up to 50% (N=33) of the elderly subjects aged 62 to 88 years immunised with H5N1 MF59C.1 adjuvanted vaccine containing A/Vietnam/1194/2004 in trial V87P1 were seroprotected at six months.

A third (booster) dose of H5N1 vaccine combined with MF59C.1 was administered 6 months after the primary vaccination series. Results are shown by SRH.

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

	Study V87P1 Adults A/Vietnam/1194/2004 booster after 2 nd dose	Study V87P2 Adults A/Vietnam/1194/2004 booster after 2 nd dose	Study V87P1 Elderly A/Vietnam/1194/2004 booster after 2 nd dose
SRH	N=71	N=13	N=38
Seroprotection rate (95% CI)*	89% (79-95)	85% (55-98)	84% (69-94)
Seroconversion rate (95% CI)**	83% (72-91)	69% (39-91)	63% (46-78)
Seroconversion fact or (95% CI)***	5.96 (4.72-7.53)	2.49 (1.56-3.98)	5.15 (3.46-7.66)

* Seroprotection: SRH area ≥ 25 mm²

** Seroconversion was defined as an SRH area ≥ 25 mm² for subjects who were seronegative at baseline (Day 1 SRH area ≤ 4 mm²) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area > 4 mm²)

*** GMRs of SRH

- Supportive data in adult and elderly populations

In two dose finding studies 80 adults received an adjuvanted pandemic preparedness vaccine (H5N3 or H9N2). Two doses of vaccine with H5N3 (A/Duck/Singapore/97) strain at 3 different dosages (7.5, 15 and 30 μ g 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 μ g 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 μ g HA/dose), were administered four weeks apart. Serologic responses obtained with the HI assay showed that 92% of subjects achieved seroprotection and 75% seroconverted after two 7.5 μ g injections.

Cross reactivity

Cross-reactive immune response elicited by H5N1 A/Vietnam/1194/2004 against A/turkey/Turkey/1/2005 and A/Indonesia/5/2005

Adults (18-60 years)

Some heterologous immune response against A/turkey/Turkey/1/2005 (NIBRG23; clade 2.2.1) and A/Indonesia/5/2005 (clade 2.1) was detectable both after the second and third vaccinations, indicating cross-reactivity of the clade 1 vaccine against clade 2 strains.

Seroprotection rate*, seroconversion rate** and the seroconversion factor*** for anti-HA antibodies to H5N1 A/turkey/Turkey/1/2005 after the 2nd dose in adults 18-60 years of age, measured by SRH and HI assays were as follows:

	Anti-HA antibody	Study V87P1 A/Vietnam/1194/ 2004 21 days after 2 nd dose N=70	Study V87P12 A/Vietnam/1194/ 2004 21 days after 2 nd dose N=60	Study V87P3 A/Vietnam/1194/ 2004 21 days after 2 nd dose N=30	Study V87P13 A/Vietnam/1194/ 2004 21 days after 2 nd dose N=197
SRH	Seroprotection rate (95% CI)*	70% (58-80)	65% (52-77)	90% (73-98)	59% (52-66)
	Seroconversion rate (95% CI)**	NA†	65% (52-77)	86% (68-96)	49% (42-56)
	Seroconversion factor(95% CI)***	NA†	4.51 (3.63-5.61)	7.67 (6.09-9.67)	2.37 (2.1-2.67)
		N=69	N=60	N=30	N=197
HI	Seroprotection rate (95% CI) ^o	36% (25-49)	28% (17-41)	24% (10-44)	23% (18-30)
	Seroconversion rate (95% CI) ^o	NA†	28% (17-41)	21% (8-40)	19% (14-25)
	Seroconversion factor (95% CI) ^{oo}	NA†	2.3 (1.67-3.16)	1.98 (1.22-3.21)	1.92 (1.64-2.25)

* Seroprotection: SRH area ≥ 25 mm²

** Seroconversion was defined as an SRH area ≥ 25 mm² for subjects who were seronegative at baseline (Day 1 SRH area ≤ 4 mm²) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area > 4 mm²)

*** GMRs of SRH

† In V87P1: baseline not tested

^o measured by HI assay ≥ 40

^{oo} GMRs of HI

MN results for the clinical studies V87P12, V87P3 and V87P13 in the Table above revealed a seroprotection rate and seroconversion rate against A/turkey/Turkey/2005 ranging from 10% (2-27) to 39% (32-46) and 10% (2-27) to 36% (29-43) respectively. MN results yielded a GMR against A/turkey/Turkey/2005 ranging from 1.59 to 2.95.

Elderly (≥ 61 years)

Seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibodies to H5N1 A/turkey/Turkey/05 after the 2nd dose in elderly subjects ≥ 61 years of age, measured by SRH and HI assays were as follows:

	Anti-HA antibody	Study V87P1 A/Vietnam/1194/2004 21 days after 2 nd dose N=37	Study V87P13 A/Vietnam/1194/2004 21 days after 2 nd dose N=207
SRH	Seroprotection rate (95% CI)*	57% (39-73)	20% (18-23)
	Seroconversion rate (95% CI)*	NA***	48% (41-55)

	Seroconversion factor (95%CI)**	NA***	1.74 (1.57-1.94)
		N=36	N=208
HI	Seroprotection rate (95%CI)°	36% (21-54)	25% (19-32)
	Seroconversion rate (95%CI)°	NA***	19% (14-25)
	Seroconversion factor (95%CI)°°	NA***	1.79 (1.56-2.06)

* measured by SRH assay ≥ 25 mm²

** geometric mean ratios of SRH

° measured by HI assay ≥ 40

°° geometric mean ratios of HI

*** In V87P1: baseline not tested

MN results for the clinical studies in the Table above revealed a seroprotection rate against A/turkey/Turkey/05 ranging from 11% (3-25) (study V87P1) to 30% (24-37) (study V87P13) and seroconversion rate of 25% (19-31) for study V87P13. MN results in study V87P13 yielded a GMR against A/turkey/Turkey/05 of 2.01 (1.78-2.26).

Cross-reactive immune response elicited by A/turkey/Turkey/1/2005 against A/Indonesia/5/2005 and A/Vietnam/1194/2004

Heterologous immune response against A/Indonesia/5/2005 (clade 2.1) was detectable in Study V87P11 after the second vaccination, indicating cross-reactivity of the clade 2.2.1 vaccine against clade 2.1 strains.

Seroprotection rate*, seroconversion rate** and the seroconversion factor*** for anti-HA antibodies to H5N1 A/Indonesia/5/2005 and A/Vietnam/1194/2004 after the 2nd dose in adults (18-60 years) and elderly (≥ 61 years), measured by SRH and HI assays were as follows:

Anti-HA antibody		V87P11 Adults (18-60 years) N=186		V87P11 Elderly (≥ 61 -89 years) ^a N=142	
		A/Indonesia/ 5/2005	A/Vietnam/ 1194/2004	A/Indonesia/ 5/2005	A/Vietnam/ 1194/2004
SRH	Seroprotection rate (95%CI)*	83 (77-88)	62 (54-69)	61 (52-69)	45 (37-54)
	Seroconversion rate (95%CI)**	79 (72-85)	60 (53-68)	64 (56-73)	44 (35-53)
	Seroconversion factor (95%CI)***	6.24 (5.44-7.16)	4.45 (3.85-5.14)	3.87 (3.31-4.53)	3.03 (2.56-3.58)
		N=194		N=148	
HI	Seroprotection rate (95%CI) °	50 (43-57)	47 (40-55)	34 (26-42)	39 (31-48)
	Seroconversion rate (95%CI) °	49 (42-56)	44 (37-51)	32 (25-41)	34 (26-42)
	Seroconversion factor (95%CI) °°	4.71 (3.74-5.93)	4.25 (3.36-5.37)	2.69 (2.18-3.32)	2.8 (2.2-3.55)

^a actual age range of population enrolled

* Seroprotection: SRH area ≥ 25 mm²

** Seroconversion was defined as an SRH area ≥ 25 mm² for subjects who were seronegative at baseline (Day 1 SRH area ≤ 4 mm²) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area > 4 mm²)

*** GMRs of SRH

° measured by HI assay ≥ 40

°° GMRs of HI

MN results for A/Indonesia/5/2005 revealed a seroprotection rate of 38% (31-45) in adults (18-60 years) and 14% (8-20) in elderly (≥ 61 years); a seroconversion rate of 58% (50-65) in adults and 30% (23-38) in elderly and finally a GMR of 4.67 (3.95-5.56) in adults and 2.19 (1.86-2.58) in elderly.

MN results for A/Vietnam/1194/2004 revealed a seroprotection rate of 10% (6-16) in adults (18-60 years) and 6% (3-11) in elderly (≥ 61 years); a seroconversion rate of 19% (13-25) in adults and 7% (4-13) in elderly and finally a GMR of 1.86 (1.63-2.12) in adults and 1.33 (1.17-1.51) in elderly.

Long term booster immune memory:

A single vaccination with H5N1 MF59C.1 adjuvanted A/Vietnam/1194/2004 vaccine induced high and rapid serological response in subjects primed 6-8 years previously with two doses of a different vaccine, having the same formulation but using the H5N3 strain.

In a phase I clinical trial (V87P3) adult subjects aged 18-65 years primed 6-8 years previously with 2 doses of MF59-adjuvanted H5N3 vaccine/A/Duck/Singapore/97, were administered 2 booster doses of H5N1 MF59C.1 adjuvanted A/Vietnam/1194/2004 vaccine. SRH results after the first dose, that mimic pre-pandemic priming plus single heterologous booster dose, revealed seroprotection and seroconversion rates of 100% (74- 100) and an 18-fold increase in SRH area (GMR).

Alternative vaccination schedules:

In a clinical trial evaluating 4 different vaccination schedules in 240 subjects 18 to 60 years of age, where the second dose occurred either 1, 2, 3 or 6 weeks after the first dose of H5N1 MF59C.1 adjuvanted A/Vietnam/1194/2004 vaccine, all vaccine schedule groups after 3 weeks from the 2nd vaccination achieved high levels of antibodies as evaluated with SRH. SRH seroprotection rates ranged from 86% to 98%, seroconversion rates from 64% to 90%, and GMR ranged from 2.92 to 4.57. The magnitude of immune response was lower in the group who received the 2nd dose 1 week later and higher in the groups with longer interval schedules.

Subjects with underlying medical or immunosuppressive conditions:

Immunogenicity of H5N1 A/turkey/Turkey/1/2005 in adults (18 to 60 years) and elderly (≥ 61 years) subjects with underlying medical conditions (Study V87_25) or immunosuppressive conditions (mainly HIV-infected subjects) (Study V87_26) in comparison to healthy adults (18-60 years) and elderly (≥ 61 years), was evaluated in two randomised, phase III controlled clinical trials (with a seasonal trivalent inactivated MF59-adjuvanted subunit influenza vaccine approved for use in elderly subjects 65 years of age and older as a comparator). In trial V87_25 and V87_26, 96 and 67 subjects, respectively, were over the age of 70 years. In both trials, immunogenicity of H5N1 A/turkey/Turkey/1/2005 was shown by HI, SRH and MN assays following both the first and second dose.

Geometric mean area*, seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibody to H5N1 A/turkey/Turkey/1/2005 measured by SRH assays 21 days after the 2nd dose were as follows:

Study V87_25				
	Adults (20- 60 years) ^a	Adults (19- 60 years) ^a	Elderly (61-84 years) ^a	Elderly (61-79 years) ^a
Anti-HA antibody (SRH)	Medical Conditions N=140	Healthy N=57	Medical Conditions N=143	Healthy N=57
Geometric Mean Area (95%CI)*	31.07 (27.43-35.19)	58.02 (48.74-69.06)	29.34 (26.07-33.01)	27.78 (22.57-34.18)
Seroprotection rate (95%CI)*	65.00 (56.5-72.9)	89.47 (78.5-96)	58.74 (50.2-66.9)	57.89 (44.1-70.9)
Seroconversion rate (95%CI)*	72.86 (64.7-80)	98.25 (90.6-99.96)	64.34 (55.9-72.2)	66.67 (52.9-78.6)

Seroconversion factor (95% CI)**	3.33 (2.94-3.77)	6.58 (5.53-7.83)	2.37 (2.10-2.66)	2.96 (2.41-3.64)
Study V87_26				
	Adults (20- 60 years) ^a	Adults (18-59 years) ^a	Elderly (61-84 years) ^a	Elderly (61-91 years) ^a
Anti-HA antibody (SRH)	Immuno-compromised N=143	Healthy N=57	Immuno-compromised N=139	Healthy N=62
Geometric Mean Area (95% CI)*	26.50 (22.49-31.22)	48.58 (40.01-58.99)	26.85 (23.01-31.33)	23.91 (18.89-30.26)
Seroprotection rate (95% CI)*	60.84 (52.3-68.9)	87.72 (76.3-94.9)	58.99 (50.3-67.3)	53.23 (40.1-66)
Seroconversion rate (95% CI)*	61.54 (53-69.5)	89.47 (78.5-96)	64.75 (56.2-72.7)	56.45 (43.3-69)
Seroconversion factor (95% CI)**	3.16 (2.69-3.73)	7.10 (5.85-8.62)	3.15 (2.70-3.68)	2.83 (2.24-3.58)

^a actual age range of population enrolled

* measured by SRH assay seroprotection: SRH area ≥ 25 mm², seroconversion: SRH area ≥ 25 mm² for subjects with a baseline SRH area ≤ 4 mm² or a minimum 50% increase in SRH area for subjects with >4 mm².

** geometric mean ratios of SRH

HI results for the two clinical studies revealed lower values than those reported in previous studies. Seroconversion rates against homologous A/turkey/Turkey/1/2005 ranged from 37.50% to 43.10% in healthy adults, and from 19.18% to 26.47% in adults with immunosuppressive or underlying medical conditions, respectively; seroconversion rates ranged from 21.43% to 30.65% in healthy elderly subjects, and from 24.49% to 27.86% in elderly subjects with immunosuppressive or underlying medical conditions. Similar trends were observed for seroprotection rates in both studies.

MN results against homologous A/turkey/Turkey/1/2005 indicate a seroconversion rate of 66.67% in healthy adults, and ranging from 33.57% to 54.14% in adults with immunosuppressive or underlying medical conditions, respectively; seroconversion rates ranged from 24.39% to 29.03% in healthy elderly subjects, and from 31.65% to 39.42% in elderly subjects with immunosuppressive or underlying medical conditions. Similar trends were observed for seroprotection rates in both studies.

In both studies V87_25 and V87_26, the lower levels of antibodies (as measured by HI, SRH and MN assays) and reduced seroprotection rates in adults and elderly (≥ 61 years old) subjects with underlying medical or immunosuppressive conditions, suggest that H5N1 A/turkey/Turkey/1/2005 may not elicit the same level of protection against A/H5N1 strain as compared to healthy adults (see section 4.4). These studies provided limited immunogenicity data in subjects with some underlying medical (in particular, renal impairment and peripheral cardiovascular disease) and immunosuppressive conditions (in particular, transplant recipients and patients under cancer treatment). In these trials, lower levels of antibodies and reduced seroprotection rates against homologous H5N1 A/turkey/Turkey/1/2005 were also measured in healthy elderly subjects, as compared to healthy adults, though previous studies showed induction of sufficiently immunogenic responses against H5N1 strains (see above for information on elderly).

Available data in paediatric populations

A clinical trial (V87P6) was conducted with a H5N1 A/Vietnam/1194/2004 vaccine combined with MF59C.1 adjuvant in 471 children from 6 months to 17 years of age. Two doses of 7.5 µg were administered three weeks apart and a third dose 12 months following the first dose. After 3 weeks from the 2nd vaccination (day 43) all age groups (i.e. 6-35 months, 3-8 years and 9-17 years) achieved high levels of antibodies to A/Vietnam/1194/2004 as evaluated with SRH and HI assays as presented in table below. In this trial no vaccine related SAEs were observed.

		Toddlers (6 to 35 months)	Children (3 to 8 years)	Adolescents (9 to 17 years)
		N=134	N=91	N=89
HI	Seroprotection rate (95% CI) Day 43	97% (92-99)	97% (91-99)	89% (80-94)
	Seroconversion factor (95% CI) Day 43 to Day 1	129 (109-151)	117 (97-142)	67 (51-88)
	Seroconversion rate (95% CI) Day 43	97% (92-99)	97% (91-99)	89% (80-94)
SRH		N=133	N=91	N=90
	Seroprotection rate (95% CI) Day 43	100% (97-100)	100% (96-100)	100% (96-100)
	Seroconversion factor (95% CI) Day 43 to Day 1	16 (14-18)	15 (13-17)	14 (12-16)
	Seroconversion rate (95% CI) Day 43	98% (95-100)	100% (96-100)	99% (94-100)

MN results against a A/Vietnam/1194/2004 indicate a seroprotection rate of 99% (95%CI: 94-100), a seroconversion rate ranging from 97% (95%CI: 91-99) to 99% (95%CI: 96-100) and a GMR ranging from 29 (95%CI: 25-35) to 50 (95%CI: 44-58).

Immunogenicity results with Focetria H1N1v (Study V111_03):

The seroprotection rate and seroconversion rate measured by HI assay and the seroconversion factor expressed as geometric mean ratio of HI for anti-HA antibody to H1N1 after administration of one and two 7.5 µg doses of Focetria was evaluated in 70 children and adolescents (9-17 years), 60 children (3-8 years), 58 children (12-35 months) and 49 infants (6-11 months). CHMP immunogenicity criteria set for adults (18-60 years) were met both after the 1st and the 2nd dose in all the above age strata (both in the overall population and in the subset seronegative at baseline).

The European medicines Agency has deferred the obligation to submit the results of studies with Foclivia in one or more subsets of the paediatric populations in active immunisation against H5N1 subtype of Influenza A virus. See section 4.2 for information on paediatric use.

Foclivia has been authorised under “Exceptional Circumstances”. This means that for scientific reasons, it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency (EMA) will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data obtained with Foclivia and with seasonal influenza vaccine containing MF59C.1 adjuvant reveal no special hazard for humans based on conventional studies of repeated dose toxicity, local tolerance, female fertility, and reproductive and developmental toxicity (through the end of the lactation period).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride,
Potassium chloride,
Potassium dihydrogen phosphate,
Disodium phosphate dihydrate,
Magnesium chloride hexahydrate,
Calcium chloride dihydrate,
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. Discard if the vaccine has been frozen. Store in the original package in order to protect from light.

6.5 Nature and contents of container

0.5 ml in single-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 before use.
After shaking, the normal appearance of Foclivia is a milky-white suspension.

Visually inspect the suspension prior to administration. In case of any particles and/or abnormal appearance, the vaccine should be discarded.

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

7. MARKETING AUTHORISATION HOLDER

Seqirus S.r.l.
Via del Pozzo 3/A, S. Martino
53035 Monteriggioni (SI)
Italy

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/577/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 October 2009
Date of latest renewal: 19 October 2014

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Foclivia suspension for injection in multidose container
Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

A/Vietnam/1194/2004 (H5N1) 7.5 micrograms**
per 0.5 ml dose

* propagated in fertilised hens' eggs from healthy chicken flocks

** expressed in microgram haemagglutinin.

Adjuvant MF59C.1 containing:

Squalene	9.75 milligrams
Polysorbate 80	1.175 milligrams
Sorbitan trioleate	1.175 milligrams
Sodium citrate	0.66 milligrams
Citric acid	0.04 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.

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

Excipient with known effect:

The vaccine contains 1.899 milligrams of sodium and 0.081 milligrams of potassium per 0.5 ml dose.

Foclivia may contain trace residues of egg and chicken proteins, ovalbumin, kanamycin sulphate, neomycin sulphate, formaldehyde and cetyltrimethylammonium bromide which are used during the manufacturing process (see section 4.3).

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 in an officially declared pandemic situation.
Foclivia should be used in accordance with Official Guidance.

4.2 Posology and method of administration

Posology

Adults and elderly (18 years of age and above): 0.5 ml at an elected date.
A second dose of vaccine should be given after an interval of at least 3 weeks.

Foclivia was evaluated in adults (aged 18 to 60 years old) and elderly (over 60 years old) following a 1, 22 day primary vaccination schedule.

Data on a third dose (booster) administered 6 months after the first dose are limited (see sections 4.8 and 5.1).

Paediatric population

The safety and efficacy of Foclivia in subjects under 18 years of age have not yet been established. Currently available data in subjects aged 6 months to 18 years of age are described in section 5.1 but no recommendation on a posology can be made.

No data are available in children aged less than 6 months.

Method of administration

Immunisation should be carried out by intramuscular injection 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 (eggs, chicken proteins, ovalbumin, kanamycin sulphate, neomycin sulphate, formaldehyde and cetyltrimethylammonium bromide) of this vaccine. However, in a pandemic situation, it may be appropriate to give this vaccine to individuals with a history of anaphylaxis as defined above, provided that facilities for resuscitation are immediately available in case of need. See section 4.4.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Caution is needed when administering this vaccine to persons with a known hypersensitivity to the active substance, to any of the excipients listed in section 6.1, to thiomersal and to residues (eggs, chicken proteins, ovalbumin, kanamycin sulphate, neomycin sulphate, formaldehyde and cetyltrimethylammonium bromide).

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

If the pandemic situation allows, immunisation should be postponed in patients with febrile illness until the fever is resolved.

The vaccine should under no circumstances be administered intravascularly or intradermally. There are no data with Foclivia using the subcutaneous route of administration. 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 bleeding.

Protection against influenza

There is no immune correlate of protection established for influenza A (H5N1).

A protective immune response may not be elicited in all vaccine recipients. In addition, antibody responses in patients with endogenous or iatrogenic immunosuppression may be insufficient to provide protection.

Some degree of cross-reactive immunity has been observed against H5N1 viruses of clades different to that of the vaccine strain. However, the degree of protection that may be elicited to H5N1 strains of other clades is unknown (see section 5.1).

Since a second dose is recommended, it should be noted that there are no safety, immunogenicity or efficacy data to support interchangeability of Foclivia with other H5N1 monovalent vaccines.

While no data are available from the use of Foclivia, cases of convulsion with and without fever have been reported in subjects vaccinated with Focetria, an MF59.1 adjuvanted H1N1 pandemic vaccine similar to Foclivia.

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).

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

4.5 Interaction with other medicinal products and other forms of interaction

Foclivia may be co-administered with non-adjuvanted seasonal influenza vaccines, and immunisation should be carried out on separate limbs.

There are no data on co-administration of Foclivia with vaccines other than non-adjuvanted seasonal influenza 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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Limited data obtained from women who became pregnant during the course of clinical trials with Foclivia or other pandemic vaccines adjuvanted with MF59C.1 were insufficient to inform vaccine-associated risks in pregnancy.

However, it is estimated that during the 2009 H1N1 pandemic more than 90,000 women were vaccinated during pregnancy with Focetria (an H1N1 pandemic vaccine similar to Foclivia) which contains the same amount of MF59C.1 as Foclivia. Post-marketing spontaneously reported adverse events and an interventional study do not suggest direct or indirect harmful effects of Focetria exposure on pregnancy. In addition, two large observational studies designed to assess the safety of Focetria exposure in pregnancy showed no increase in the rates of gestational diabetes, preeclampsia, abortions, stillbirth, low birth weight, prematurity, neonatal deaths, and congenital malformations among almost 10,000 vaccinated pregnant women and their offspring compared with unvaccinated controls.

Health care providers need to assess the benefits and potential risks of administering Foclivia vaccine to pregnant women, taking into consideration official recommendations.

Breast-feeding

There are no data regarding the use of Foclivia during breast-feeding. The potential benefits and risks to the mother and infant should be considered before administering Foclivia.

Fertility

There are no data concerning human fertility. A study in female rabbits did not indicate reproductive or developmental toxicity of Foclivia. Male fertility has not been assessed in animals (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

- Clinical trials

Adverse reactions from clinical trial in adults and elderly (above 18 years old)

The incidence of adverse reactions has been evaluated in seven clinical trials in healthy subjects involving over 4300 adults and elderly receiving H5N1 vaccine combined with MF59C.1 adjuvant (at least 7.5 µg haemagglutinin, HA) containing either the A/turkey/Turkey/1/2005 or the A/Vietnam/1194/2004 strain. There were 3872 subjects 18-60 years of age, 365 subjects 61-70 years of age, and 89 subjects greater than 70 years of age. The safety profile across clinical trials using H5N1 vaccine containing either the A/turkey/Turkey/1/2005 or the A/Vietnam/1194/2004 strain is comparable (see section 5.1). Clinical trials in 80 subjects receiving adjuvanted vaccine with an H5N3 or an H9N2 strain showed a similar safety profile.

Across all trials, there was a general trend towards decreased reports of solicited local adverse reactions after the second vaccination compared with the first.

Irrespective of antigen dose, almost all solicited systemic adverse reactions were reported on the day of vaccination (day 1) or during the 3 days immediately following.

Data on safety of a booster dose are limited to three trials performed with H5N1 MF59C.1 adjuvanted vaccine containing A/Vietnam/1194/2004 (V87P1, V87P2) or A/turkey/Turkey/1/2005 (V87P1E1) that included 116 adults (18-60 years) and 56 elderly subjects (≥61 years). No increase in solicited adverse reactions was reported when a booster dose was administered 6 or 18 months after the initial dosing series. A slight increase in solicited adverse reactions in adults was reported when a booster dose was administered 18 months after the initial dosing series. In the elderly, the reported solicited adverse reactions increased with the third booster dose only when compared with the second dose.

Tabulated list of adverse reactions

The adverse reaction rates reported after any vaccination dose (i.e. 1st, 2nd or booster) were similar and are listed according to the following MedDRA frequency convention and system organ class: 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).

MedDRA System Organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Rare (≥1/10,000 to <1/1,000)
Nervous system disorders	Headache		

Gastrointestinal disorders		Nausea	
Skin and subcutaneous tissue disorders		Sweating	
Musculoskeletal and connective tissue disorders	Myalgia	Arthralgia	
General disorders and administration site conditions	Injection site swelling, Injection site pain, Injection site induration, Injection site redness, Fatigue, Chills, Malaise	Injection site ecchymosis, Fever	Anaphylaxis

The majority of these reactions usually disappear within 1-2 days without treatment.

Clinical trials in special populations

Adverse reactions in special populations have been evaluated in two clinical trials, V87_25 and V87_26, involving adult (18-60 years) and elderly (≥ 61 years) subjects who were either healthy or with underlying medical conditions or immunosuppressive conditions.

H5N1 MF59C.1 adjuvanted A/turkey/Turkey/1/2005 vaccine								
Study V87_25					Study V87_26			
	Medical conditions		Healthy		Immunocompromised		Healthy	
	Adults (20-60 years)*	Elderly (61-84 years)*	Adults (19-60 years)*	Elderly (61-79 years)*	Adults (20-60 years)*	Elderly (61-84 years)*	Adults (18-59 years)*	Elderly (61-91 years)*
No. of subjects	N=145	N=149	N=59	N=58	N=147	N=148	N=58	N=62

*actual age range of population enrolled

Across studies V87_25 and V87_26, the safety of H5N1 A/turkey/Turkey/1/2005 in healthy adult and elderly subjects was consistent with existing safety data from previous clinical trials. However, in immunocompromised subjects 18 through 60 years of age, slightly higher rates of nausea (13.0%) were reported. In addition, higher rates of arthralgia (up to 23.3%) were reported in both adult and elderly subjects, who were immunocompromised or with underlying medical conditions.

The following solicited adverse reactions were additionally collected in these two studies and reported with the following frequencies across subjects who received H5N1 A/turkey/Turkey/1/2005 irrespective of age or health status: diarrhoea (up to 11.9%), loss of appetite (up to 10.9%) and vomiting (up to 1.7%). In both studies, subjects with underlying medical and immunosuppressive conditions reported higher frequencies of diarrhoea, loss of appetite and vomiting compared to healthy subjects (irrespective of age).

Adverse reactions from clinical trial in children aged 6 months to 17 years

A clinical trial (Study V87P6) was conducted with a H5N1 A/Vietnam/1194/2004 vaccine combined with MF59C.1 adjuvant (N=334) vs seasonal influenza vaccine (N=137).

Regardless of age, reactogenicity was higher after the first dose than after the second vaccination. Reactogenicity after the third dose, administered 12 months following the second dose, was higher than after both first and second doses. The percentages of subjects reporting local adverse reactions

were higher in the older age groups, mainly due to the higher reports for pain. In toddlers, erythema and tenderness were the most frequently reported solicited local adverse reactions; irritability and unusual crying were the most frequently reported solicited systemic adverse reactions. In children and adolescents, pain was the most frequently reported solicited local adverse reaction, and fatigue and headache were the most frequently reported solicited systemic adverse reactions. Across all ages, the frequency of fever after any dose was not more than 6%.

	Study V87P6 H5N1 MF59C.1 adjuvanted A/Vietnam/1194/2004 vaccine		
	First dose	Second dose (21 days after first dose)	Third dose (12 months after second dose)
Toddlers (6 to 35 months)	N=145	N=138	N=124
Any	76%	68%	80%
Local	47%	46%	60%
Systemic	59%	51%	54%
Fever $\geq 38^{\circ}\text{C}$ ($\geq 40^{\circ}\text{C}$)	0%	0%	0%
Any Other Adverse Event	54%	49%	35%
Children (3 to 8 years)	N=96	N=93	N=85
Any	72%	68%	79%
Local	66%	58%	74%
Systemic	32%	33%	45%
Fever $\geq 38^{\circ}\text{C}$ ($\geq 40^{\circ}\text{C}$)	4%	2%	6%
Any Other Adverse Event	36%	31%	19%
Adolescents(9 to 17 years)	N=93	N=91	N=83
Any	91%	82%	89%
Local	81%	70%	81%
Systemic	69%	52%	69%
Fever $\geq 38^{\circ}\text{C}$ ($\geq 40^{\circ}\text{C}$)	0%	1%	2%
Any Other Adverse Event	30%	27%	22%

Focetria (an MF59.1 adjuvanted H1N1 pandemic vaccine similar to Foclivia).

Adverse reactions in the week following vaccination with Focetria H1N1v from 77 children 3-8 years old and 80 children and adolescents 9-17 years old receiving the 7.5 μg formulation were reported as follows:

	<i>Injection 1</i>	<i>Injection 2</i>
<i>Children (3 to 8 years of age)</i>	<i>N= 77</i>	<i>N= 75</i>
<i>Any adverse reaction</i>	<i>74%</i>	<i>69%</i>
<i>Local</i>	<i>62%</i>	<i>56%</i>
<i>Systemic</i>	<i>39%</i>	<i>35%</i>
<i>Fever $\geq 38^{\circ}\text{C}$ to 38.9°C</i>	<i>4%</i>	<i>1%</i>
<i>Fever 39°C to 39.9°C</i>	<i>0%</i>	<i>1%</i>
<i>Fever $\geq 40^{\circ}\text{C}$</i>	<i>0%</i>	<i>0%</i>
<i>Any other AE</i>	<i>14%</i>	<i>17%</i>
<i>Adolescents (9 to 17 years of age)</i>	<i>N= 80</i>	<i>N= 79</i>
<i>Any adverse reaction</i>	<i>79%</i>	<i>66%</i>
<i>Local</i>	<i>70%</i>	<i>58%</i>
<i>Systemic</i>	<i>45%</i>	<i>30%</i>

<i>Fever ≥ 38°C to 38.9°C</i>	<i>3%</i>	<i>1%</i>
<i>Fever 39°C to 39.9°C</i>	<i>0%</i>	<i>0%</i>
<i>Fever ≥ 40° C</i>	<i>0%</i>	<i>0%</i>
<i>Any other AE</i>	<i>13%</i>	<i>10%</i>

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 with Focetria H1N1v from 73 infants 6-11 months old and 73 toddlers 12-35 months old, receiving the 7.5 µg formulation were reported as follows:

	<i>Injection 1</i>	<i>Injection 2</i>
<i>Infants (6 to 11 months of age)</i>	<i>N= 73</i>	<i>N= 68</i>
<i>Any adverse reaction</i>	<i>79%</i>	<i>65%</i>
<i>Local</i>	<i>44%</i>	<i>26%</i>
<i>Systemic</i>	<i>70%</i>	<i>56%</i>
<i>Fever ≥ 38°C to 38.9°C</i>	<i>11%</i>	<i>9%</i>
<i>Fever 39°C to 39.9°C</i>	<i>3%</i>	<i>4%</i>
<i>Fever ≥ 40° C</i>	<i>0%</i>	<i>0%</i>
<i>Any other AE</i>	<i>32%</i>	<i>31%</i>
<i>Toddlers (12 to 35 months of age)</i>	<i>N= 73</i>	<i>N= 71</i>
<i>Any adverse reaction</i>	<i>70%</i>	<i>71%</i>
<i>Local</i>	<i>51%</i>	<i>49%</i>
<i>Systemic</i>	<i>60%</i>	<i>49%</i>
<i>Fever ≥ 38°C to 38.9°C</i>	<i>10%</i>	<i>11%</i>
<i>Fever 39°C to 39.9°C</i>	<i>4%</i>	<i>1%</i>
<i>Fever ≥ 40° C</i>	<i>1%</i>	<i>0%</i>
<i>Any other AE</i>	<i>21%</i>	<i>24%</i>

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 146 infants and toddlers 6 to 35 months of age:
Tenderness, erythema, irritability, unusual crying, sleepiness, diarrhoea, vomiting and change in eating habits. Induration and ecchymosis were very common reactions in toddlers but were less common in infants.

- Post-marketing surveillance

No post-marketing surveillance data are available following Foclivia administration.

The following adverse events were reported from post-marketing surveillance with Focetria (an H1N1 pandemic vaccine similar to Foclivia) which contains the same amount of adjuvant MF59C.1 as Foclivia, approved for use in children 6 months of age and above, adults and the elderly:

Blood and lymphatic system disorders

Lymphadenopathy.

Immune system disorders

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

Nervous system disorders

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

Cardiac disorders

Palpitation, tachycardia.

Respiratory disorders

Cough.

Gastrointestinal disorders

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

Skin and subcutaneous tissue disorders

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

Musculoskeletal, connective tissue and bone disorders

Muscular weakness, pain in extremities.

General disorders and administration site conditions

Asthenia.

The following additional adverse events were reported from post-marketing surveillance with seasonal non-adjuvanted trivalent vaccines in all age groups and a seasonal trivalent MF59-adjuvanted subunit influenza vaccine approved for use in elderly subjects 65 years of age and older:

Blood and lymphatic system disorders

Thrombocytopenia (in some cases reversible platelet counts less than 5000 mm³).

Nervous system disorders

Neurological disorders, such as encephalomyelitis and Guillain Barré syndrome.

Vascular disorders

Vasculitis which may be associated with transient renal involvement.

Skin and subcutaneous tissue disorders

Erythema multiforme.

General disorders and administration site conditions

Extensive swelling of injected limb lasting more than one week, injection-site cellulitis-like reaction (some cases of swelling, pain, and redness extending more than 10 cm and lasting more than 1 week).

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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#)

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccine, ATC Code: J07BB02

Clinical efficacy and safety

Pandemic preparedness 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 pandemic preparedness vaccine will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical efficacy and safety data obtained with pandemic preparedness vaccines are relevant for the pandemic vaccines.

Immune response to H5N1 vaccine combined with MF59C.1 adjuvant containing A/Vietnam/1194/2004 or A/turkey/Turkey/1/2005 strain.

Adults (18-60 years)

A Phase II clinical trial (V87P1) was conducted with H5N1 MF59C.1 adjuvanted vaccine containing A/Vietnam/1194/2004 in 312 healthy adults. Two doses of vaccine containing 7.5 µg Haemagglutinin(HA)/dose were administered three weeks apart to 156 subjects. Immunogenicity was assessed in 149 subjects.

In a phase III clinical trial (V87P13), 2693 adult subjects were enrolled and 2566 received two doses of H5N1 MF59C.1 adjuvanted vaccine containing A/Vietnam/1194/2004 7.5 µg HA/dose administered three weeks apart. Immunogenicity was assessed in a subset (N=197) of subjects.

In a third clinical trial (V87P11) 194 adult subjects received two doses of H5N1 MF59C.1 adjuvanted vaccine containing A/turkey/Turkey/1/2005 7.5 µg HA/dose administered three weeks apart. Immunogenicity was assessed in 182 subjects.

The seroprotection rate*, seroconversion rate** and the seroconversion factor*** for anti-HA antibody to H5N1 A/Vietnam/1194/2004 and to H5N1 A/turkey/Turkey/1/2005 in the adults measured by Single Radial Haemolysis (SRH) assay was as follows:

Anti-HA antibody (SRH)	Study V87P1 A/Vietnam/1194/2004 21 days after 2 nd dose N=149	Study V87P13 A/Vietnam/1194/2004 21 days after 2 nd dose N=197	Study V87P11 A/turkey/Turkey/1/2005 21 days after 2 nd dose N=182
Seroprotection rate (95%CI)*	85% (79-91)	91% (87-95)	91% (85-94)
Seroconversion rate (95%CI)**	85% (78-90)	78% (72-84)	85% (79-90)
Seroconversion factor (95%CI)***	7.74 (6.6-9.07)	4.03 (3.54-4.59)	6 (5.2-6.93)

Anti-HA antibody (SRH)	Study V87P13 A/Vietnam/1194/2004 21 days after 2 nd dose N=69	Study V87P13 A/Vietnam/1194/2004 21 days after 2 nd dose N=128	-
Baseline Serostatus	< 4 mm ²	≥ 4 mm ²	-
Seroprotection rate (95%CI)*	87% (77-94)	94% (88-97)	-
Seroconversion rate (95%CI)**	87% (77-94)	73% (65-81)	-

Seroconversion factor (95% CI)***	8.87 (7.09-11)	2.71 (2.38-3.08)	-
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* Seroprotection: SRH area ≥ 25 mm²

** Seroconversion was defined as an SRH area ≥ 25 mm² for subjects who were seronegative at baseline (Day 1 SRH area ≤ 4 mm²) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area > 4 mm²)

*** geometric mean ratios (GMRs) of SRH

MicroNeutralization (MN) results against A/Vietnam/1194/2004 (Studies V87P1 and V87P13) indicate a seroprotection and seroconversion rate ranging from 67% (60-74) to 85% (78-90) and 65% (58-72) to 83% (77-89), respectively. Immune response to vaccination assessed by MN assay is in line with results obtained with SRH.

In Study V87P11 MN results against homologous A/turkey/Turkey/1/2005 indicate a seroprotection and seroconversion rate of 85% (79-90) and 93% (89-96), respectively. Immune response to vaccination assessed by MN assay is in line with results obtained with SRH.

Persistence of antibodies after primary vaccination in this population was assessed by Hemagglutination Inhibition (HI), SRH, and MN assays. Compared to the antibody levels obtained at day 43 after completion of primary vaccination schedules, antibody levels at day 202 were reduced by 1/5 to 1/2 from their prior levels.

Elderly (≥ 61 years)

The seroprotection rate*, seroconversion rate** and the seroconversion factor*** for anti-HA antibody to H5N1 MF59C.1 adjuvanted vaccine (A/Vietnam/1194/2004 and A/turkey/Turkey/1/2005) in subjects aged 61 years and older (limited number of subjects were above 70 years of age; N=123) measured by SRH assay assessed in two clinical studies were as follows:

Anti-HA antibody (SRH)	Study V87P1 A/Vietnam/1194/2004 21 days after 2 nd dose N=84 ^a	Study V87P13 A/Vietnam/1194/2004 21 days after 2 nd dose N=210 ^b	Study V87P11 A/turkey/Turkey/1/2005 21 days after 2 nd dose N=132 ^c
Seroprotection rate (95% CI)*	80% (70-88)	82% (76-87)	82% (74-88)
Seroconversion rate (95% CI)**	70% (59-80)	63% (56-69)	70% (61-77)
Seroconversion factor (95% CI)***	4.96 (3.87-6.37)	2.9 (2.53-3.31)	3.97 (3.36-4.69)

Anti-HA antibody (SRH)	Study V87P13 A/Vietnam/1194/2004 21 days after 2 nd dose N=66	Study V87P13 A/Vietnam/1194/2004 21 days after 2 nd dose N=143
Baseline Serostatus	< 4 mm ²	≥ 4 mm ²
Seroprotection rate (95% CI)*	82% (70-90)	82% (75-88)
Seroconversion rate (95% CI)**	82% (70-90)	54% (45-62)
Seroconversion factor (95% CI)***	8.58 (6.57-11)	1.91 (1.72-2.12)

^a Ages 62-88 years; ^b Ages 61-68 years; ^c Ages 61-89 years

* Seroprotection: SRH area ≥ 25 mm²

** Seroconversion was defined as an SRH area ≥ 25 mm² for subjects who were seronegative at baseline (Day 1 SRH area ≤ 4 mm²) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area > 4 mm²)

*** GMRs of SRH

MN results against A/Vietnam/1194/2004 (Studies V87P1 and V87P13) indicate a seroprotection and seroconversion rate ranging from 57% (50-64) to 79% (68-87) and 55% (48-62) to 58% (47-69) respectively. MN results, similar to SRH results, demonstrated strong immune response after completion of priming vaccination series in a population of elderly subjects.

In Study V87P11, MN results against homologous A/turkey/Turkey/1/2005 indicate a seroprotection and seroconversion rate of 68% (59-75) and 81% (74-87), respectively. Immune response to vaccination assessed by MN assay is similar to SRH results.

Persistence of antibodies after primary vaccination in this population as assessed by HI, SRH, and MN tests reduced from 1/2 to 1/5 of their post-vaccination level at day 202 as compared to day 43 after completion of primary schedules as assessed by HI, SRH, and MN tests. Up to 50% (N=33) of the elderly subjects aged 62 to 88 years immunised with H5N1 MF59C.1 adjuvanted vaccine containing A/Vietnam/1194/2004 in trial V87P1 were seroprotected at six months.

A third (booster) dose of H5N1 vaccine combined with MF59C.1 was administered 6 months after the primary vaccination series. Results are shown by SRH.

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

	Study V87P1 Adults A/Vietnam/1194/2004 booster after 2 nd dose	Study V87P2 Adults A/Vietnam/1194/ 2004 booster after 2 nd dose	Study V87P1 Elderly A/Vietnam/1194/2004 booster after 2 ^{n^d} dose
SRH	N=71	N=13	N=38
Seroprotection rate (95% CI)*	89% (79-95)	85% (55-98)	84% (69-94)
Seroconversion rate (95% CI)**	83% (72-91)	69% (39-91)	63% (46-78)
Seroconversion factor (95% CI)***	5.96 (4.72-7.53)	2.49 (1.56-3.98)	5.15 (3.46-7.66)

* Seroprotection: SRH area ≥ 25 mm²

** Seroconversion was defined as an SRH area ≥ 25 mm² for subjects who were seronegative at baseline (Day 1 SRH area ≤ 4 mm²) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area > 4 mm²)

*** GMRs of SRH

- Supportive data in adult and elderly populations

In two dose finding studies 80 adults received an adjuvanted pandemic preparedness vaccine (H5N3 or H9N2).

Two doses of vaccine with H5N3 (A/Duck/Singapore/97) strain at 3 different dosages (7.5, 15 and 30 μ g 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 μ g 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 μ g HA/dose), were administered four weeks apart. Serologic responses obtained with the HI assay showed that 92% of subjects achieved seroprotection and 75% seroconverted after two 7.5 μ g injections.

Cross reactivity

Cross-reactive immune response elicited by H5N1 A/Vietnam/1194/2004 against A/turkey/Turkey/1/2005 and A/Indonesia/5/2005

Adults (18-60 years)

Some heterologous immune response against A/turkey/Turkey/1/2005 (NIBRG23; clade 2.2.1) and A/Indonesia/5/2005 (clade 2.1) was detectable both after the second and third vaccinations, indicating cross-reactivity of the clade 1 vaccine against clade 2 strains.

Seroprotection rate*, seroconversion rate** and the seroconversion factor*** for anti-HA antibodies to H5N1 A/turkey/Turkey/1/2005 after the 2nd dose in adults 18-60 years of age, measured by SRH and HI assays were as follows:

	Anti-HA antibody	Study V87P1 A/Vietnam/1194/ 2004 21 days after 2 nd dose N=70	Study V87P12 A/Vietnam/1194/ 2004 21 days after 2 nd dose N=60	Study V87P3 A/Vietnam/1194/ 2004 21 days after 2 nd dose N=30	Study V87P13 A/Vietnam/1194/ 2004 21 days after 2 nd dose N=197
SRH	Seroprotection rate (95% CI)*	70% (58-80)	65% (52-77)	90% (73-98)	59% (52-66)
	Seroconversion rate (95% CI)**	NA†	65% (52-77)	86% (68-96)	49% (42-56)
	Seroconversion factor(95% CI)***	NA†	4.51 (3.63-5.61)	7.67 (6.09-9.67)	2.37 (2.1-2.67)
		N=69	N=60	N=30	N=197
HI	Seroprotection rate (95% CI)°	36% (25-49)	28% (17-41)	24% (10-44)	23% (18-30)
	Seroconversion rate (95% CI)°	NA†	28% (17-41)	21% (8-40)	19% (14-25)
	Seroconversion factor (95% CI)°°	NA†	2.3 (1.67-3.16)	1.98 (1.22-3.21)	1.92 (1.64-2.25)

* Seroprotection: SRH area ≥ 25 mm²

** Seroconversion was defined as an SRH area ≥ 25 mm² for subjects who were seronegative at baseline (Day 1 SRH area ≤ 4 mm²) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area > 4 mm²)

*** GMRs of SRH

† In V87P1: baseline not tested

° measured by HI assay ≥ 40

°° GMRs of HI

MN results for the clinical studies V87P12, V87P3 and V87P13 in the Table above revealed a seroprotection rate and seroconversion rate against A/turkey/Turkey/2005 ranging from 10% (2-27) to 39% (32-46) and 10% (2-27) to 36% (29-43) respectively. MN results yielded a GMR against A/turkey/Turkey/2005 ranging from 1.59 to 2.95.

Elderly (≥ 61 years)

Seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibodies to H5N1 A/turkey/Turkey/05 after the 2nd dose in elderly subjects ≥ 61 years of age, measured by SRH and HI assays were as follows:

	Anti-HA antibody	Study V87P1 A/Vietnam/1194/2004 21 days after 2 nd dose N=37	Study V87P13 A/Vietnam/1194/2004 21 days after 2 nd dose N=207
SRH	Seroprotection rate (95%CI)*	57% (39-73)	20% (18-23)
	Seroconversion rate (95%CI)*	NA***	48% (41-55)
	Seroconversion factor (95%CI)**	NA***	1.74 (1.57-1.94)
		N=36	N=208
HI	Seroprotection rate (95%CI) ^o	36% (21-54)	25% (19-32)
	Seroconversion rate (95%CI) ^o	NA***	19% (14-25)
	Seroconversion factor (95%CI) ^{oo}	NA***	1.79 (1.56-2.06)

* measured by SRH assay ≥ 25 mm²

** geometric mean ratios of SRH

^o measured by HI assay ≥ 40

^{oo} geometric mean ratios of HI

*** In V87P1: baseline not tested

MN results for the clinical studies in the Table above revealed a seroprotection rate against A/turkey/Turkey/05 ranging from 11% (3-25) (study V87P1) to 30% (24-37) (study V87P13) and seroconversion rate of 25% (19-31) for study V87P13. MN results in study V87P13 yielded a GMR against A/turkey/Turkey/05 of 2.01 (1.78-2.26).

Cross-reactive immune response elicited by A/turkey/Turkey/1/2005 against A/Indonesia/5/2005 and A/Vietnam/1194/2004

Heterologous immune response against A/Indonesia/5/2005 (clade 2.1) was detectable in Study V87P11 after the second vaccination, indicating cross-reactivity of the clade 2.2.1 vaccine against clade 2.1 strains.

Seroprotection rate*, seroconversion rate** and the seroconversion factor*** for anti-HA antibodies to H5N1 A/Indonesia/5/2005 and A/Vietnam/1194/2004 after the 2nd dose in adults (18-60 years) and elderly (≥ 61 years), measured by SRH and HI assays were as follows:

Anti-HA antibody		V87P11 Adults (18-60 years) N=186		V87P11 Elderly (≥ 61 -89 years) ^a N=142	
		A/Indonesia/ 5/2005	A/Vietnam/ 1194/2004	A/Indonesia/ 5/2005	A/Vietnam/ 1194/2004
SRH	Seroprotection rate (95%CI)*	83 (77-88)	62 (54-69)	61 (52-69)	45 (37-54)
	Seroconversion rate (95%CI)**	79 (72-85)	60 (53-68)	64 (56-73)	44 (35-53)
	Seroconversion factor (95%CI)***	6.24 (5.44-7.16)	4.45 (3.85-5.14)	3.87 (3.31-4.53)	3.03 (2.56-3.58)
		N=194		N=148	
HI	Seroprotection rate (95%CI) ^o	50 (43-57)	47 (40-55)	34 (26-42)	39 (31-48)
	Seroconversion rate (95%CI) ^o	49 (42-56)	44 (37-51)	32 (25-41)	34 (26-42)
	Seroconversion factor (95%CI) ^{oo}	4.71 (3.74-5.93)	4.25 (3.36-5.37)	2.69 (2.18-3.32)	2.8 (2.2-3.55)

- ^a actual age range of population enrolled
- * Seroprotection: SRH area ≥ 25 mm²
- ** Seroconversion was defined as an SRH area ≥ 25 mm² for subjects who were seronegative at baseline (Day 1 SRH area ≤ 4 mm²) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area > 4 mm²)
- *** GMRs of SRH
- o measured by HI assay ≥ 40
- oo GMRs of HI

MN results for A/Indonesia/5/2005 revealed a seroprotection rate of 38% (31-45) in adults (18-60 years) and 14% (8-20) in elderly (≥ 61 years); a seroconversion rate of 58% (50-65) in adults and 30% (23-38) in elderly and finally a GMR of 4.67 (3.95-5.56) in adults and 2.19 (1.86-2.58) in elderly.

MN results for A/Vietnam/1194/2004 revealed a seroprotection rate of 10% (6-16) in adults (18-60 years) and 6% (3-11) in elderly (≥ 61 years); a seroconversion rate of 19% (13-25) in adults and 7% (4-13) in elderly and finally a GMR of 1.86 (1.63-2.12) in adults and 1.33 (1.17-1.51) in elderly.

Long term booster immune memory:

A single vaccination with H5N1 MF59C.1 adjuvanted A/Vietnam/1194/2004 vaccine induced high and rapid serological response in subjects primed 6-8 years previously with two doses of a different vaccine, having the same formulation but using the H5N3 strain.

In a phase I clinical trial (V87P3) adult subjects aged 18-65 years primed 6-8 years previously with 2 doses of MF59-adjuvanted H5N3 vaccine/A/Duck/Singapore/97, were administered 2 booster doses of H5N1 MF59C.1 adjuvanted A/Vietnam/1194/2004 vaccine. SRH results after the first dose, that mimic pre-pandemic priming plus single heterologous booster dose, revealed seroprotection and seroconversion rates of 100% (74- 100) and an 18-fold increase in SRH area (GMR).

Alternative vaccination schedules:

In a clinical trial evaluating 4 different vaccination schedules in 240 subjects 18 to 60 years of age, where the second dose occurred either 1, 2, 3 or 6 weeks after the first dose of H5N1 MF59C.1 adjuvanted A/Vietnam/1194/2004 vaccine, all vaccine schedule groups after 3 weeks from the 2nd vaccination achieved high levels of antibodies as evaluated with SRH. SRH seroprotection rates ranged from 86% to 98%, seroconversion rates from 64% to 90%, and GMR ranged from 2.92 to 4.57. The magnitude of immune response was lower in the group who received the 2nd dose 1 week later and higher in the groups with longer interval schedules.

Subjects with underlying medical or immunosuppressive conditions:

Immunogenicity of H5N1 A/turkey/Turkey/1/2005 in adults (18 to 60 years) and elderly (≥ 61 years) subjects with underlying medical conditions (Study V87_25) or immunosuppressive conditions (mainly HIV-infected subjects) (Study V87_26) in comparison to healthy adults (18-60 years) and elderly (≥ 61 years), was evaluated in two randomised, phase III controlled clinical trials (with a seasonal trivalent inactivated MF59-adjuvanted subunit influenza vaccine approved for use in elderly subjects 65 years of age and older as a comparator). In trial V87_25 and V87_26, 96 and 67 subjects, respectively, were over the age of 70 years. In both trials, immunogenicity of H5N1 A/turkey/Turkey/1/2005 was shown by HI, SRH and MN assays following both the first and second dose.

Geometric mean area*, seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibody to H5N1 A/turkey/Turkey/1/2005 measured by SRH assays 21 days after the 2nd dose were as follows:

Study V87_25				
	Adults (20- 60 years) ^a	Adults (19- 60 years) ^a	Elderly (61-84 years) ^a	Elderly (61-79 years) ^a
Anti-HA antibody (SRH)	Medical Conditions N=140	Healthy N=57	Medical Conditions N=143	Healthy N=57
Geometric Mean Area (95%CI)*	31.07 (27.43-35.19)	58.02 (48.74-69.06)	29.34 (26.07-33.01)	27.78 (22.57-34.18)
Seroprotection rate (95%CI)*	65.00 (56.5-72.9)	89.47 (78.5-96)	58.74 (50.2-66.9)	57.89 (44.1-70.9)
Seroconversion rate (95%CI)*	72.86 (64.7-80)	98.25 (90.6-99.96)	64.34 (55.9-72.2)	66.67 (52.9-78.6)
Seroconversion factor (95%CI)**	3.33 (2.94-3.77)	6.58 (5.53-7.83)	2.37 (2.10-2.66)	2.96 (2.41-3.64)
Study V87_26				
	Adults (20- 60 years) ^a	Adults (18-59 years) ^a	Elderly (61-84 years) ^a	Elderly (61-91 years) ^a
Anti-HA antibody (SRH)	Immuno- compromised N=143	Healthy N=57	Immuno- compromised N=139	Healthy N=62
Geometric Mean Area (95%CI)*	26.50 (22.49-31.22)	48.58 (40.01-58.99)	26.85 (23.01-31.33)	23.91 (18.89-30.26)
Seroprotection rate (95%CI)*	60.84 (52.3-68.9)	87.72 (76.3-94.9)	58.99 (50.3-67.3)	53.23 (40.1-66)
Seroconversion rate (95%CI)*	61.54 (53-69.5)	89.47 (78.5-96)	64.75 (56.2-72.7)	56.45 (43.3-69)
Seroconversion factor (95%CI)**	3.16 (2.69-3.73)	7.10 (5.85-8.62)	3.15 (2.70-3.68)	2.83 (2.24-3.58)

^a actual age range of population enrolled

* measured by SRH assay seroprotection: SRH area ≥ 25 mm², seroconversion: SRH area ≥ 25 mm² for subjects with a baseline SRH area ≤ 4 mm² or a minimum 50% increase in SRH area for subjects with >4 mm².

** geometric mean ratios of SRH

HI results for the two clinical studies revealed lower values than those reported in previous studies. Seroconversion rates against homologous A/turkey/Turkey/1/2005 ranged from 37.50% to 43.10% in healthy adults, and from 19.18% to 26.47% in adults with immunosuppressive or underlying medical conditions, respectively; seroconversion rates ranged from 21.43% to 30.65% in healthy elderly subjects, and from 24.49% to 27.86% in elderly subjects with immunosuppressive or underlying medical conditions. Similar trends were observed for seroprotection rates in both studies.

MN results against homologous A/turkey/Turkey/1/2005 indicate a seroconversion rate of 66.67% in healthy adults, and ranging from 33.57% to 54.14% in adults with immunosuppressive or underlying medical conditions, respectively; seroconversion rates ranged from 24.39% to 29.03% in healthy elderly subjects, and from 31.65% to 39.42% in elderly subjects with immunosuppressive or underlying medical conditions. Similar trends were observed for seroprotection rates in both studies.

In both studies V87_25 and V87_26, the lower levels of antibodies (as measured by HI, SRH and MN assays) and reduced seroprotection rates in adults and elderly (≥ 61 years old) subjects with underlying medical or immunosuppressive conditions, suggest that H5N1 A/turkey/Turkey/1/2005 may not elicit the same level of protection against A/H5N1 strain as compared to healthy adults (see section 4.4). These studies provided limited immunogenicity data in subjects with some underlying medical (in particular, renal impairment and peripheral cardiovascular disease) and immunosuppressive conditions (in particular, transplant recipients and patients under cancer treatment). In these trials, lower levels of antibodies and reduced seroprotection rates against homologous H5N1 A/turkey/Turkey/1/2005 were also measured in healthy elderly subjects, as compared to healthy adults, though previous studies

showed induction of sufficiently immunogenic responses against H5N1 strains (see above for information on elderly).

Available data in paediatric populations

A clinical trial (V87P6) was conducted with a H5N1 A/Vietnam/1194/2004 vaccine combined with MF59C.1 adjuvant in 471 children from 6 months to 17 years of age. Two doses of 7.5 µg were administered three weeks apart and a third dose 12 months following the first dose. After 3 weeks from the 2nd vaccination (day 43) all age groups (i.e. 6-35 months, 3-8 years and 9-17 years) achieved high levels of antibodies to A/Vietnam/1194/2004 as evaluated with SRH and HI assays as presented in table below. In this trial no vaccine related SAEs were observed.

		Toddlers (6 to 35 months)	Children (3 to 8 years)	Adolescents (9 to 17 years)
		N=134	N=91	N=89
HI	Seroprotection rate (95% CI) Day 43	97% (92-99)	97% (91-99)	89% (80-94)
	Seroconversion factor (95% CI) Day 43 to Day 1	129 (109-151)	117 (97-142)	67 (51-88)
	Seroconversion rate (95% CI) Day 43	97% (92-99)	97% (91-99)	89% (80-94)
SRH		N=133	N=91	N=90
	Seroprotection rate (95% CI) Day 43	100% (97-100)	100% (96-100)	100% (96-100)
	Seroconversion factor (95% CI) Day 43 to Day 1	16 (14-18)	15 (13-17)	14 (12-16)
	Seroconversion rate (95% CI) Day 43	98% (95-100)	100% (96-100)	99% (94-100)

MN results against a A/Vietnam/1194/2004 indicate a seroprotection rate of 99% (95%CI: 94-100), a seroconversion rate ranging from 97% (95%CI: 91-99) to 99% (95%CI: 96-100) and a GMR ranging from 29 (95%CI: 25-35) to 50 (95%CI: 44-58).

Immunogenicity results with Focetria H1N1v (Study V111_03):

The seroprotection rate and seroconversion rate measured by HI assay and the seroconversion factor expressed as geometric mean ratio of HI for anti-HA antibody to H1N1 after administration of one and two 7.5 µg doses of Focetria was evaluated in 70 children and adolescents (9-17 years), 60 children (3-8 years), 58 children (12-35 months) and 49 infants (6-11 months). CHMP immunogenicity criteria set for adults (18-60 years) were met both after the 1st and the 2nd dose in all the above age strata (both in the overall population and in the subset seronegative at baseline).

The European medicines Agency has deferred the obligation to submit the results of studies with Foclivia in one or more subsets of the paediatric populations in active immunisation against H5N1 subtype of Influenza A virus. See section 4.2 for information on paediatric use.

Foclivia has been authorised under “Exceptional Circumstances”.

This means that for scientific reasons, it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency (EMA) will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data obtained with Foclivia and with seasonal influenza vaccine containing MF59C.1 adjuvant reveal no special hazard for humans based on conventional studies of repeated dose toxicity, local tolerance, female fertility, and reproductive and developmental toxicity (through the end of the lactation period).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride,
Potassium chloride,
Potassium dihydrogen phosphate,
Disodium phosphate dihydrate,
Magnesium chloride hexahydrate,
Calcium chloride dihydrate,
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. Discard if the vaccine has been frozen. 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. After shaking, the normal appearance of Foclivia is a milky-white suspension. Visually inspect the suspension prior to administration. In case of any particles and/or abnormal appearance, the vaccine should be discarded.

Although Foclivia 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. 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

Seqirus S.r.l.
Via del Pozzo 3/A, S. Martino
53035 Monteriggioni (SI)
Italy

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/577/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 October 2009
Date of latest renewal: 19 October 2014

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**
- E. SPECIFIC OBLIGATIONS TO COMPLETE POST AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES**

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Seqirus Vaccines Ltd
Gaskill Road, Speke, Liverpool
L24 9GR
UK

Name and address of the manufacturer responsible for batch release

Seqirus Netherlands B.V.
Paasheuvelweg 28
1105BJ Amsterdam
Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

Foclivia 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 Foclivia takes due account of the officially declared pandemic strain.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, 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

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Outside of the pandemic period, the normal PSUR periodicity and format will be maintained, with a specific review of AESI and possible adverse events related to adjuvants. This should include data from ongoing studies, or actual use if applicable, of the pandemic preparedness strains and any safety data relevant to the adjuvant system.

During a pandemic situation, the resources must be concentrated on a timely and effective monitoring of the safety profile of the influenza vaccines used during the pandemic. Moreover, a 6-monthly cycle may be too long to allow assessment of the safety of a vaccine for which high levels of exposure are expected within a short period of time. Therefore, 6-monthly or annual PSURs falling within the pandemic period will be replaced by monthly “simplified PSURs” (S-PSUR) accompanied by a summary of vaccine distribution.

- Frequency of submission:

- The clock should start from the first Monday after shipment of the first batch of vaccine.

- First data-lock point is 30 days later.
- S-PSUR submission to the Rapporteur and CHMP members on Day 45.
- Rapporteur's assessment report is circulated to CHMP members on Day 50.
- CHMP report is circulated to the vaccine manufacturer on Day 55.
- Reporting to be monthly for the first 6 months.
- Periodicity should be reviewed by the MAH and the (Co-)Rapporteur at 6 monthly intervals.

When it has been agreed by the CHMP that the S-PSUR is no longer necessary, a full PSUR covering the period since the data lock point of the last routine PSUR will be submitted within a time frame to be agreed with the Rapporteur.

- Format of the simplified PSUR:

Only spontaneously reported data should be included in the PSUR. The report should include the following Tables of aggregate data (using the pre-defined templates attached in Annex 2).

1. An overview for all spontaneous cases per country, stratified according to type of report (medically confirmed or non-medically confirmed) and seriousness, for the period covered by the report and cumulatively.
2. An overview for all spontaneous adverse reactions by SOC, High Level Term (HLT) and Preferred Term (PT), stratified according to type of report (medically confirmed or non-medically confirmed) and including the number of fatal reports, for the period covered by the report and cumulatively.
3. Adverse Events of Special Interest stratified according to type of report (medically confirmed or non-medically confirmed). AESIs will be defined as follows:
 - Neuritis: PT "Neuritis"
 - Convulsion: narrow SMQ "Convulsions"
 - Anaphylaxis: narrow SMQ "Anaphylactic reaction" and narrow SMQ "Angioedema"
 - Encephalitis: narrow SMQ "Non-infectious encephalitis"
 - Vasculitis: narrow SMQ "Vasculitis"
 - Guillain-Barré syndrome: narrow SMQ "Guillain-Barré syndrome"
 - Demyelination: narrow SMQ "Demyelination" (as GBS is also included in this SMQ, there will be an overlap in the number of cases for these two categories).
 - Bell's palsy: PT "Bell's palsy"
 - Vaccination failure: PT "Vaccination failure".
4. Serious unlisted adverse reactions (SOC, HLT, PTs) stratified according to type of report (medically confirmed or non-medically confirmed), for the period covered by the report and cumulatively.
5. All spontaneous adverse reactions by age group, per SOC, HLT and PT, stratified according to type of report (medically confirmed or non-medically confirmed), for the period covered by the report and cumulatively. The following age groups will be used: < 2 years, 2-8 years, > 9 years.
6. All spontaneous adverse reactions (SOC, HLT, PT) occurring in pregnant women, stratified according to type of report (medically confirmed or non-medically confirmed), for the period covered by the report and cumulatively.

The following principles should be followed when compiling the data:

- Except for Table 1, all tables will be based on number of reactions (presented on PT level, sorted by System Organ Class [SOC] and High Level Term [HLT]) and not number of cases.
- All tables will be based on generic and not product-specific data¹. Product-specific data can be evaluated during signal work-up.
- “Cumulatively” means since the use of the vaccine; events not reported during the period of interest should not be presented in the tables.
- All non-medically confirmed events are those that have been entered into the database by the data-lock point. Those which have not yet been entered should be reported in the following S-PSUR.
- A line listing of fatal cases will be provided in an Annex.

A short summary should be provided in which validated signals and areas of concern are highlighted, taking into account information arising from the prospective cohort study described in 4.5. In the event of multiple signals, signal work-up may be prioritised and appropriate timelines for submission of a full signal evaluation report should be provided.

Vaccine distribution report

To put the safety report into context, a summary of vaccine distribution should be included and should provide details of the number of doses of vaccine distributed in

- EU member states for the reporting period by batch number,
- EU member states cumulatively and
- the rest of the world.

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

• **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
During the pandemic, the applicant will collect clinical safety and effectiveness data of the pandemic vaccine and submit this information to the CHMP for evaluation.	Depending on and after implementation of vaccine when first pandemic will take place.
During the pandemic, the applicant will conduct a prospective cohort study as identified in the Pharmacovigilance plan	Depending on and after implementation of vaccine

¹ Based on the assumption that product name will not be provided in a significant proportion of cases.

	when first pandemic will take place.
--	--------------------------------------

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

Foclivia suspension for injection in pre-filled syringe
Pandemic Influenza Vaccine (surface antigen, inactivated, adjuvanted)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose (0.5 ml) contains: Active Ingredients: Influenza virus surface antigens (haemagglutinin and neuraminidase), propagated in fertilised hen's eggs from healthy chicken flocks, and adjuvanted with MF59C.1, of strain:

A/Vietnam/1194/2004 (H5N1) 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 (sodium citrate, citric acid).

3. LIST OF EXCIPIENTS

Sodium chloride, potassium chloride, potassium dihydrogen phosphate, disodium phosphate dihydrate, magnesium chloride hexahydrate, calcium chloride dihydrate, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.

1 x single dose (0.5 ml) pre-filled syringe with needle
1 x single dose (0.5 ml) pre-filled syringe without needle
10 x single dose (0.5 ml) pre-filled syringes with needle
10 x single dose (0.5 ml) pre-filled syringe without needle

5. METHOD AND ROUTE(S) OF ADMINISTRATION

To be administered intramuscularly into the deltoid muscle.

Warning: Do not inject intravascularly or intradermally.

Read the package leaflet before use.

Gently shake before use.

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

Keep out of the sight and reach 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

Seqirus S.r.l.
Via del Pozzo 3/A, S. Martino
53035 Monteriggioni (SI)
Italy.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/577/001 1 prefilled syringe with needle
EU/1/09/577/002 10 prefilled syringes with needle
EU/1/09/577/005 1 prefilled syringe without needle
EU/1/09/577/006 10 prefilled syringes without needle

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:

SN:

NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARDBOARD BOX FOR 1-DOSE VIAL

1. NAME OF THE MEDICINAL PRODUCT

Foclivia suspension for injection
Pandemic Influenza Vaccine (surface antigen, inactivated, adjuvanted)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose (0.5 ml) contains: Active Ingredients: Influenza virus surface antigens (haemagglutinin and neuraminidase), propagated in fertilised hen's eggs from healthy chicken flocks, and adjuvanted with MF59C.1, of strain:

A/Vietnam/1194/2004 (H5N1) 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 (sodium citrate, citric acid).

3. LIST OF EXCIPIENTS

Sodium chloride, potassium chloride, potassium dihydrogen phosphate, disodium phosphate dihydrate, magnesium chloride hexahydrate, calcium chloride dihydrate, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.

Vial
10 x 1 dose
1 dose (0.5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

To be administered intramuscularly into the deltoid muscle.

Warning: Do not inject intravascularly or intradermally.

Read the package leaflet before use.

Gently shake before use.

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

Keep out of the sight and reach 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

Seqirus S.r.l.
Via del Pozzo 3/A, S. Martino
53035 Monteriggioni (SI)
Italy.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/577/003

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARDBOARD BOX FOR 10-DOSE VIAL

1. NAME OF THE MEDICINAL PRODUCT

Foclivia suspension for injection in multidose container
Pandemic Influenza Vaccine (surface antigen, inactivated, adjuvanted)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose (0.5 ml) contains: Active Ingredients: Influenza virus surface antigens (haemagglutinin and neuraminidase), propagated in fertilised hen's eggs from healthy chicken flocks, and adjuvanted with MF59C.1, of strain:

A/Vietnam/1194/2004 (H5N1) 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 (sodium citrate, citric acid).

3. LIST OF EXCIPIENTS

Sodium chloride, potassium chloride, potassium dihydrogen phosphate, disodium phosphate dihydrate, magnesium chloride hexahydrate, calcium chloride dihydrate, thiomersal, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.

Vial
10 x 10 doses
1 dose (0.5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

To be administered intramuscularly into the deltoid muscle.

Warning: Do not inject intravascularly or intradermally.

Read the package leaflet before use.

Gently shake before use.

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

Keep out of the sight and reach 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

Seqirus S.r.l.
Via del Pozzo 3/A, S. Martino
53035 Monteriggioni (SI)
Italy.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/577/004

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
LABEL FOR SYRINGE AND 1-DOSE VIAL**

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

Foclivia injection
Pandemic influenza vaccine (surface antigen, inactivated, adjuvanted)
I.M. injection into the deltoid muscle

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

1 dose (0.5 ml)

6. OTHER

Seqirus S.r.l. - Italy
Store in a refrigerator.

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

Foclivia injection
Pandemic Influenza Vaccine (surface antigen, inactivated, adjuvanted)
I.M. injection into the deltoid muscle

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

5 ml vial containing 10 doses (0.5 ml/dose)

6. OTHER

Seqirus S.r.l. - Italy
Store in a refrigerator.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Foclivia suspension for injection in pre-filled syringe

Pandemic Influenza Vaccine (H5N1) (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 you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

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

1. What Foclivia is and what it is used for

Foclivia is a vaccine intended to be given to prevent influenza (flu) in an officially declared pandemic.

Pandemic flu is a type of influenza that happens at intervals that vary from less than 10 years to many decades. It spreads rapidly around the world. The signs of pandemic flu are similar to those of ordinary flu but may be more serious.

It is for use in adults (from 18 to 60 years old) and elderly (over 60 years) to prevent flu caused by the H5N1 type of the virus.

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

As with all vaccines, Foclivia may not fully protect all persons who are vaccinated.

2. What you need to know before you receive Foclivia

Foclivia should not be given if you:

- have experienced serious allergic reaction (i.e. life-threatening) to any of the constituents of Foclivia,
- are allergic (hypersensitive) to influenza vaccines or any of the ingredients of Foclivia,
- are allergic to eggs, chicken protein, ovalbumin,
- are allergic to kanamycin sulphate and neomycin sulphate (antibiotics), formaldehyde, 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, you may still be given the vaccine. This is as long as medical treatment is available straight away, in case you have an allergic reaction.

Warnings and precautions

Talk to your doctor or nurse before having this vaccine:

- if you feel feverish,
- if you have any illness or infection,
- if you are having immunosuppressive therapy, e.g. corticosteroid treatment or chemotherapy for cancer, or if you have any condition which makes you prone to infections (immunodeficiency conditions).

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

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

Fainting can occur following, or even before, any needle injection. Therefore, tell the doctor or nurse if you fainted with a previous injection.

Foclivia may not fully protect everyone who is vaccinated, especially elderly subjects and those with weakened immune systems, such as HIV patients, or those with underlying long term medical problems, such as diabetes, lung disease or heart problems. Tell your doctor if you have a weak immune system or an underlying long term medical problem.

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

Other medicines and Foclivia

Tell your doctor or nurse if you are taking or have recently taken or might take any other medicines, including medicines obtained without a prescription or have recently received any other vaccine. Foclivia can be given at the same time as non-adjuvanted seasonal influenza vaccines. There is no information on administration of Foclivia with non-influenza vaccines. If administration of Foclivia with other vaccines 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

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or nurse for advice before taking this vaccine. Your doctor needs to assess the benefits and potential risks of giving you the vaccine.

Driving and using machines

Some side effects listed in Section 4. "Possible side effects" may affect your ability to drive or use tools or machines.

Foclivia contains sodium and potassium

Foclivia contains less than 1 mmol sodium (23 mg) and less than 1 mmol of potassium (39 mg) per dose. It is essentially sodium- and potassium-free.

3. How Foclivia is given

Your doctor or nurse administers the vaccine in accordance with official recommendations. A dose (0.5 ml) of the vaccine will be injected into the upper arm (deltoid muscle) or upper thigh, depending on the muscle mass.

A second dose of vaccine should be given after an interval of at least 3 weeks.

4. Possible side effects

Like all medicines, Foclivia 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.

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

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

- Pain at the site of injection
- Hardening of the skin at the injection site
- Injection site redness
- Injection site swelling
- Aching muscles
- Headache
- Fatigue
- Generally feeling unwell
- Shivering

Common (affects 1 to 10 users in 100):

- Bruising of the skin at the injection site
- Aching joints
- Fever and nausea
- Sweating

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

- Anaphylaxis (severe allergic reactions)

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

Undesirable effects in patients with underlying long term medical problems such as diabetes, lung disease or heart problems and weakened immune systems (immunocompromised) such as HIV patients

Nausea, aching joints, diarrhoea and loss of appetite were reported very commonly in this population. In addition, vomiting was commonly reported.

Side effects from clinical study in children (6 months to 17 years of age)

General side effects reported very commonly in the 6 months to 35 months of age group were injection site redness, muscle ache, irritability and unusual crying. Very commonly reported reactions in the 36 months to 17 years of age group were pain, headache and fatigue.

Other rare side effects observed after routine use

The side effects listed below have occurred in the days or weeks after vaccination with another vaccine called Focetria H1N1v similar to Foclivia. These side effects may occur with Foclivia.

- 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
- Diarrhoea
- Headache, dizziness, drowsiness, fainting.
- Neurological disorders such as
 - Severe stabbing or throbbing pain along one or more nerves
 - Tingling
 - Fits
 - Neuritis (inflammation of nerves)
- Swollen lymph nodes, palpitations (irregular or forceful heart beat), tachycardia (faster than normal heart beat), weakness, pain in the extremities, cough and asthenia (unusual weakness).
- 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.
- Angioedema (abnormal swelling of the skin, usually around the eyes, lips, tongue, hands or feet, due to an allergic reaction).

Data in children and adolescents suggest a slight decrease in side effects 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 vaccines given routinely every year to prevent seasonal flu. These side effects may occur with Foclivia.

- Low blood platelet count which can result in bleeding or bruising.
- Vasculitis (inflammation of the blood vessels which can cause skin rashes, joint pain and kidney problems).
- Erythema multiforme (type of allergic skin reaction that occurs in response to medications, infections, or illness).
- Neurological disorders such as encephalomyelitis (inflammation of the central nervous system), and a type of paralysis known as Guillain-Barré Syndrome.
- Swelling, pain and redness at the injection site extending to more than 10 cm and lasting more than one week (Injection site cellulitis-like reaction).
- Extensive swelling of injected limb lasting more than one week.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly [via the national reporting system listed in Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Foclivia

Keep this vaccine out of the sight and reach of children.

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

Store in a refrigerator (2°C - 8°C). Do not freeze. Discard if the vaccine has been frozen. Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Foclivia contains

- Active substance:

The active ingredients of the vaccine are purified viral proteins (called haemagglutinin and neuraminidase). They are isolated from the surface of influenza virus particles, which are grown in fertilised hen's eggs from healthy chicken flocks and inactivated with formaldehyde. These viral proteins are prepared from the strain of influenza virus that complies with the World Health Organisation recommendations and EU decision in an officially declared Pandemic situation.

One dose (0.5 ml) of the vaccine contains at least 7.5 micrograms of haemagglutinin from the following recommended influenza virus strain:

A/Vietnam/1194/2004 (H5N1)

- Adjuvant:

The vaccine contains an 'adjuvant' (a compound containing squalene) to stimulate a better response. The adjuvant includes also polysorbate 80 and sorbitan trioleate in a citrate buffer (sodium citrate, citric acid).

- Other ingredients:

The other ingredients are: sodium chloride, potassium chloride, potassium dihydrogen phosphate, disodium phosphate dihydrate, magnesium chloride hexahydrate, calcium chloride dihydrate and water for injections.

What Foclivia looks like and contents of the pack

Foclivia is a milky-white liquid.

It is provided in a ready-to-use syringe, containing a single dose (0.5 ml) for injection, in box of 1 or 10, with or without needle.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Seqirus S.r.l.

Via del Pozzo 3/A, S. Martino

53035 Monteriggioni (SI)

Italy

Manufacturer

Seqirus Netherlands B.V.

Paasheuvelweg 28

1105BJ Amsterdam

Netherlands

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

Foclivia has been authorised under "Exceptional Circumstances".

This means that for scientific reasons, it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency (EMA) will review any new information on the medicine every year and this leaflet will be updated as necessary.

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

The following information is intended for healthcare professionals only:

Instructions for administration of the vaccine:

The vaccine should under no circumstances be administered intravascularly or intradermally. There are no data with Foclivia using the subcutaneous route of administration.

When using a pre-filled syringe without a needle supplied with a Luer Lock system, remove the tip cap by unscrewing it in a counter-clockwise direction. Once the tip cap is removed, attach a needle to the syringe by screwing it on in a clockwise direction until it locks. Once the needle is locked in place, remove the needle protector and administer the vaccine.

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

Gently shake before use. After shaking, the normal appearance of Foclivia is a milky-white suspension.

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

Package leaflet: Information for the user

Foclivia suspension for injection

Pandemic Influenza Vaccine (H5N1) (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 you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

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

1. What Foclivia is and what it is used for

Foclivia is a vaccine intended to be given to prevent influenza (flu) in an officially declared pandemic.

Pandemic flu is a type of influenza that happens at intervals that vary from less than 10 years to many decades. It spreads rapidly around the world. The signs of pandemic flu are similar to those of ordinary flu but may be more serious.

It is for use in adults (from 18 to 60 years old) and elderly (over 60 years) to prevent flu caused by the H5N1 type of the virus.

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

As with all vaccines, Foclivia may not fully protect all persons who are vaccinated.

2. What you need to know before you receive Foclivia

Foclivia should not be given if you:

- have experienced serious allergic reaction (i.e. life-threatening) to any of the constituents of Foclivia,
- are allergic (hypersensitive) to influenza vaccines or any of the ingredients of Foclivia,
- are allergic to eggs, chicken protein, ovalbumin,
- are allergic to kanamycin sulphate and neomycin sulphate (antibiotics), formaldehyde, 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, you may still be given the vaccine. This is as long as medical treatment is available straight away, in case you have an allergic reaction.

Warnings and precautions

Talk to your doctor or nurse before having this vaccine:

- if you feel feverish,
- if you have any illness or infection,
- if you are having immunosuppressive therapy, e.g. corticosteroid treatment or chemotherapy for cancer, or if you have any condition which makes you prone to infections (immunodeficiency conditions).

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

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

Fainting can occur following, or even before, any needle injection. Therefore, tell the doctor or nurse if you fainted with a previous injection.

Foclivia may not fully protect everyone who is vaccinated, especially elderly subjects and those with weakened immune systems, such as HIV patients, or those with underlying long term medical problems, such as diabetes, lung disease or heart problems. Tell your doctor if you have a weak immune system or an underlying long term medical problem.

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

Other medicines and Foclivia

Tell your doctor or nurse if you are taking or have recently taken or might take any other medicines, including medicines obtained without a prescription or have recently received any other vaccine. Foclivia can be given at the same time as non-adjuvanted seasonal influenza vaccines. There is no information on administration of Foclivia with non-influenza vaccines. If administration of Foclivia with other vaccines 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

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or nurse for advice before taking this vaccine. Your doctor needs to assess the benefits and potential risks of giving you the vaccine.

Driving and using machines

Some side effects listed in Section 4. "Possible side effects" may affect your ability to drive or use tools or machines.

Foclivia contains sodium and potassium

Foclivia contains less than 1 mmol sodium (23 mg) and less than 1 mmol of potassium (39 mg) per dose. It is essentially sodium- and potassium-free.

3. How Foclivia is given

Your doctor or nurse administers the vaccine in accordance with official recommendations. A dose (0.5 ml) of the vaccine will be injected into the upper arm (deltoid muscle) or upper thigh, depending on the muscle mass.

A second dose of vaccine should be given after an interval of at least 3 weeks.

4. Possible side effects

Like all medicines, Foclivia 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.

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

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

- Pain at the site of injection
- Hardening of the skin at the injection site
- Injection site redness
- Injection site swelling
- Aching muscles
- Headache
- Fatigue
- Generally feeling unwell
- Shivering

Common (affects 1 to 10 users in 100):

- Bruising of the skin at the injection site
- Aching joints
- Fever and nausea
- Sweating

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

- Anaphylaxis (severe allergic reactions)

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

Undesirable effects in patients with underlying long term medical problems such as diabetes, lung disease or heart problems and weakened immune systems (immunocompromised) such as HIV patients

Nausea, aching joints, diarrhoea and loss of appetite were reported very commonly in this population. In addition, vomiting was commonly reported.

Side effects from clinical study in children (6 months to 17 years of age)

General side effects reported very commonly in the 6 months to 35 months of age group were injection site redness, muscle ache, irritability and unusual crying. Very commonly reported reactions in the 36 months to 17 years of age group were pain, headache and fatigue.

Other rare side effects observed after routine use

The side effects listed below have occurred in the days or weeks after vaccination with another vaccine called Focetria H1N1v similar to Foclivia. These side effects may occur with Foclivia.

- 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
- Diarrhoea
- Headache, dizziness, drowsiness, fainting.
- Neurological disorders such as
 - Severe stabbing or throbbing pain along one or more nerves
 - Tingling
 - Fits
 - Neuritis (inflammation of nerves)
- Swollen lymph nodes, palpitations (irregular or forceful heart beat), tachycardia (faster than normal heart beat), weakness, pain in the extremities, cough and asthenia (unusual weakness).
- 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.
- Angioedema (abnormal swelling of the skin, usually around the eyes, lips, tongue, hands or feet, due to an allergic reaction).

Data in children and adolescents suggest a slight decrease in side effects 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 vaccines given routinely every year to prevent seasonal flu. These side effects may occur with Foclivia.

- Low blood platelet count which can result in bleeding or bruising.
- Vasculitis (inflammation of the blood vessels which can cause skin rashes, joint pain and kidney problems).
- Erythema multiforme (type of allergic skin reaction that occurs in response to medications, infections, or illness).
- Neurological disorders such as encephalomyelitis (inflammation of the central nervous system), and a type of paralysis known as Guillain-Barré Syndrome.
- Swelling, pain and redness at the injection site extending to more than 10 cm and lasting more than one week (Injection site cellulitis-like reaction).
- Extensive swelling of injected limb lasting more than one week.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly [via the national reporting system listed in Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Foclivia

Keep this vaccine out of the sight and reach of children.

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

Store in a refrigerator (2°C - 8°C). Do not freeze. Discard if the vaccine has been frozen. Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Foclivia contains

- Active substance:

The active ingredients of the vaccine are purified viral proteins (called haemagglutinin and neuraminidase). They are isolated from the surface of influenza virus particles, which are grown in fertilised hen's eggs from healthy chicken flocks and inactivated with formaldehyde. These viral proteins are prepared from the strain of influenza virus that complies with the World Health Organisation recommendations and EU decision in an officially declared Pandemic situation.

One dose (0.5 ml) of the vaccine contains at least 7.5 micrograms of haemagglutinin from the following recommended influenza virus strain:

A/Vietnam/1194/2004 (H5N1)

- Adjuvant:

The vaccine contains an 'adjuvant' (a compound containing squalene) to stimulate a better response. The adjuvant includes also polysorbate 80 and sorbitan trioleate in a citrate buffer (sodium citrate, citric acid).

- Other ingredients:

The other ingredients are: sodium chloride, potassium chloride, potassium dihydrogen phosphate, disodium phosphate dihydrate, magnesium chloride hexahydrate, calcium chloride dihydrate and water for injections.

What Foclivia looks like and contents of the pack

Foclivia is a milky-white liquid.

It is provided in a vial containing a single dose (0.5 ml) for injection.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Seqirus S.r.l.

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53035 Monteriggioni (SI)

Italy

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Foclivia has been authorised under "Exceptional Circumstances".

This means that for scientific reasons, it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency (EMA) will review any new information on the medicine every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

Single dose vial: 1 vial containing a single dose (0.5 ml) for injection

Instructions for administration of the vaccine:

The vaccine should under no circumstances be administered intravascularly or intradermally. There are no data with Foclivia using the subcutaneous route of administration.

Gently shake before use. After shaking, the normal appearance of Foclivia is a milky-white suspension.

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

Package leaflet: Information for the user

Foclivia suspension for injection in multidose container

Pandemic Influenza Vaccine (H5N1) (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 you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

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

1. What Foclivia is and what it is used for

Foclivia is a vaccine intended to be given to prevent influenza (flu) in an officially declared pandemic.

Pandemic flu is a type of influenza that happens at intervals that vary from less than 10 years to many decades. It spreads rapidly around the world. The signs of pandemic flu are similar to those of ordinary flu but may be more serious.

It is for use in adults (from 18 to 60 years old) and elderly (over 60 years) to prevent flu caused by the H5N1 type of the virus.

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

As with all vaccines, Foclivia may not fully protect all persons who are vaccinated.

2. What you need to know before you receive Foclivia

Foclivia should not be given if you:

- have experienced serious allergic reaction (i.e. life-threatening) to any of the constituents of Foclivia,
- are allergic (hypersensitive) to influenza vaccines or any of the ingredients of Foclivia,
- are allergic to eggs, chicken protein, ovalbumin,
- are allergic to kanamycin sulphate and neomycin sulphate (antibiotics), formaldehyde, 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, you may still be given the vaccine. This is as long as medical treatment is available straight away, in case you have an allergic reaction.

Warnings and precautions

Talk to your doctor or nurse before having this vaccine:

- if you feel feverish,
- if you have any illness or infection,
- if you are having immunosuppressive therapy, e.g. corticosteroid treatment or chemotherapy for cancer, or if you have any condition which makes you prone to infections (immunodeficiency conditions).

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

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

Fainting can occur following, or even before, any needle injection. Therefore, tell the doctor or nurse if you fainted with a previous injection.

Foclivia may not fully protect everyone who is vaccinated, especially elderly subjects and those with weakened immune systems, such as HIV patients, or those with underlying long term medical problems, such as diabetes, lung disease or heart problems. Tell your doctor if you have a weak immune system or an underlying long term medical problem.

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

Other medicines and Foclivia

Tell your doctor or nurse if you are taking or have recently taken or might take any other medicines, including medicines obtained without a prescription or have recently received any other vaccine.

Foclivia can be given at the same time as non-adjuvanted seasonal influenza vaccines. There is no information on administration of Foclivia with non-influenza vaccines. If administration of Foclivia with other vaccines 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

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or nurse for advice before taking this vaccine. Your doctor needs to assess the benefits and potential risks of giving you the vaccine.

Driving and using machines

Some side effects listed in Section 4. "Possible side effects" may affect your ability to drive or use tools or machines.

Foclivia contains thiomersal

Foclivia 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.

Foclivia contains sodium and potassium

Foclivia contains less than 1 mmol sodium (23 mg) and less than 1 mmol of potassium (39 mg) per dose. It is essentially sodium- and potassium-free.

3. How Foclivia is given

Your doctor or nurse administers the vaccine in accordance with official recommendations. A dose (0.5 ml) of the vaccine will be injected into the upper arm (deltoid muscle) or upper thigh,

depending on the muscle mass.

A second dose of vaccine should be given after an interval of at least 3 weeks.

4. Possible side effects

Like all medicines, Foclivia 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.

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

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

- Pain at the site of injection
- Hardening of the skin at the injection site
- Injection site redness
- Injection site swelling
- Aching muscles
- Headache
- Fatigue
- Generally feeling unwell
- Shivering

Common (affects 1 to 10 users in 100):

- Bruising of the skin at the injection site
- Aching joints
- Fever and nausea
- Sweating

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

- Anaphylaxis (severe allergic reactions)

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

Undesirable effects in patients with underlying long term medical problems such as diabetes, lung disease or heart problems and weakened immune systems (immunocompromised) such as HIV patients

Nausea, aching joints, diarrhoea and loss of appetite were reported very commonly in this population. In addition, vomiting was commonly reported.

Side effects from clinical study in children (6 months to 17 years of age)

General side effects reported very commonly in the 6 months to 35 months of age group were injection site redness, muscle ache, irritability and unusual crying. Very commonly reported reactions in the 36 months to 17 years of age group were pain, headache and fatigue.

Other rare side effects observed after routine use

The side effects listed below have occurred in the days or weeks after vaccination with another vaccine called Focetria H1N1v similar to Foclivia. These side effects may occur with Foclivia.

- 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
 - Diarrhoea
- Headache, dizziness, drowsiness, fainting.
- Neurological disorders such as
 - Severe stabbing or throbbing pain along one or more nerves
 - Tingling
 - Fits
 - Neuritis (inflammation of nerves)
- Swollen lymph nodes, palpitations (irregular or forceful heart beat), tachycardia (faster than normal heart beat), weakness, pain in the extremities, cough and asthenia (unusual weakness).
- 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.
- Angioedema (abnormal swelling of the skin, usually around the eyes, lips, tongue, hands or feet, due to an allergic reaction).

Data in children and adolescents suggest a slight decrease in side effects 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 vaccines given routinely every year to prevent seasonal flu. These side effects may occur with Foclivia.

- Low blood platelet count which can result in bleeding or bruising.
- Vasculitis (inflammation of the blood vessels which can cause skin rashes, joint pain and kidney problems).
- Erythema multiforme (type of allergic skin reaction that occurs in response to medications, infections, or illness).
- Neurological disorders such as encephalomyelitis (inflammation of the central nervous system), and a type of paralysis known as Guillain-Barré Syndrome.
- Swelling, pain and redness at the injection site extending to more than 10 cm and lasting more than one week (Injection site cellulitis-like reaction).
- Extensive swelling of injected limb lasting more than one week.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Foclivia

Keep this vaccine out of the sight and reach of children.

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

Store in a refrigerator (2°C - 8°C). Do not freeze. Discard if the vaccine has been frozen. Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Foclivia contains

- Active substance:

The active ingredients of the vaccine are purified viral proteins (called haemagglutinin and neuraminidase). They are isolated from the surface of influenza virus particles, which are grown in fertilised hen's eggs from healthy chicken flocks and inactivated with formaldehyde. These viral proteins are prepared from the strain of influenza virus that complies with the World Health Organisation recommendations and EU decision in an officially declared Pandemic situation.

One dose (0.5 ml) of the vaccine contains at least 7.5 micrograms of haemagglutinin from the following recommended influenza virus strain:

A/Vietnam/1194/2004 (H5N1)

- Adjuvant:

The vaccine contains an 'adjuvant' (a compound containing squalene) to stimulate a better response. The adjuvant includes also polysorbate 80 and sorbitan trioleate in a citrate buffer (sodium citrate, citric acid).

- Other ingredients:

The other ingredients are: thiomersal, sodium chloride, potassium chloride, potassium dihydrogen phosphate, disodium phosphate dihydrate, magnesium chloride hexahydrate, calcium chloride dihydrate and water for injections.

What Foclivia looks like and contents of the pack

Foclivia is a milky-white liquid.

It is provided in a vial containing ten doses (0.5 ml each) for injection.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Seqirus S.r.l.

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53035 Monteriggioni (SI)

Italy

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Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

Multidose vial: Vial containing 10 doses (0.5 ml each) for injection.

Instructions for administration of the vaccine:

The vaccine should under no circumstances be administered intravascularly or intradermally. There are no data with Foclivia using the subcutaneous route of administration.

Gently shake the multidose vial each time before withdrawing a dose (0.5 ml) of the vaccine into a syringe. After shaking, the normal appearance of Foclivia is a milky-white suspension. Although Foclivia 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. 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.