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 micrograms 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.

Foclivia may contain trace residues of egg and chicken proteins, ovalbumin, kanamycin sulphate, neomycin sulphate, formaldehyde, hydrocortisone 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
Individuals 6 months of age and older: administer two doses (0.5 ml each), at least 3 weeks apart.

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

Paediatric population

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

Method of administration
The vaccine is administered by intramuscular injection, preferably in the anterolateral aspect of the thigh in infants or in the deltoid muscle region of the upper arm in older individuals.

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, hydrocortisone 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 administrating 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, hydrocortisone 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.

Immunocompromised individuals
Immunocompromised individuals, whether due to the use of immunosuppressive therapy, a genetic defect, HIV infection, or other causes, may have reduced immune response to active immunisation.

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.

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).

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.

Excipients with known effect
Sodium
This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'

Potassium
This vaccine contains potassium, less than 1 mmol (39 mg) per dose, that is to say essentially 'potassium-free'.

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.

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 (see section 5.3). Male fertility has not been assessed in animals.

4.7 Effects on ability to drive and use machines

Foclivia has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of H5N1 vaccine combined with MF59C.1 adjuvant (7.5 or 15 micrograms haemagglutinin, HA) containing either the A/turkey/Turkey/1/2005 or the A/Vietnam/1194/2004 strain has been evaluated in nine clinical trials in healthy subjects involving 5055 adults, elderly and children. There were 4041 adult subjects 18 to 60 years of age and 540 elderly subjects 61 years of age and above. In the paediatric population, there were 214 subjects 6 to 35 months of age, 167 subjects 3 to 8 years of age and 93 subjects 9 to 17 years of age.

The overall safety profile was similar across the adult, elderly and paediatric populations.

Clinical trials in 383 subjects receiving MF59C.1 adjuvanted vaccine with an H1N1, H5N3 or H9N2 strain showed a similar safety profile to the H5N1 trials.

Irrespective of antigen dose, antigen subtype or age group, most local and systemic adverse reactions after administration were of short duration, with onset close to the time of vaccination, and were mild or moderate in severity. Across all trials, there was a general trend towards decreased reports of local adverse reactions after the second vaccination compared with the first.

Tabulated list of adverse reactions

In adults 18 to 60 years, the most frequently reported (≥10%) adverse reactions were injection site pain (59%), myalgia (34%), headache (26%), injection site redness (24%), fatigue (24%), injection site induration (21%), injection site swelling (15%), chills (13%) and maliase (13%).

In elderly subjects (≥ 61 years), the most frequently reported (≥10%) adverse reactions were injection site pain (35%), myalgia (24%), injection site redness (17%), headache (16%), chills (12%), fatigue (10%) and malaise (10%).

In children and adolescents 3 to 17 years of age, the most frequently reported (≥10%) adverse reactions were injection site pain (95%), headache (61%), myalgia (60%), fatigue (41%), injection site redness (60%), injection site induration (34%), injection site swelling (34%), malaise (32%), nausea (25%), sweating (18%), chills (19%), diarrhoea (18%) and injection site ecchymosis (16%).

In infants and children 6 to 35 months of age, the most frequently reported (≥10%) adverse reactions were injection site redness (62%), irritability (57%), tenderness (55%), unusual crying (48%), sleepiness (45%), injection site induration (38%), injection site swelling (37%) change in eating habits (36%), diarrhoea (34%), fever (27%), injection site ecchymosis (19%), vomiting (10%), sweating, (10%) and unusual sweating (10%).

The solicited and unsolicited adverse reactions reported after any vaccination dose (i.e. first, second or booster) across subjects age, 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)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)
Immune system disorders				Anaphylaxis
Metabolism and nutrition disorders	Change in eating habits[1]	Loss of appetite		
Nervous system disorders	Headache			
Gastrointestinal disorders	Nausea[2], Diarrhoea[2], Vomiting[2]			
Skin and subcutaneous tissue disorders	Sweating[2], Unusual sweating[1]		Urticaria	
Musculoskeletal and connective tissue disorders	Myalgia	Arthralgia		
General disorders and administration site conditions	Injection site swelling, Injection site pain, Injection site tenderness[1], Injection site induration, Injection site redness, Injection site ecchymosis[2], Fatigue, Chills/Shivering, Malaise, Sleepiness[1], Irritability[1], Unusual crying[1], Fever[3]	Injection site hemorrhage		

[1] Reported only in paediatric subjects 6-35 months
[2] Reported as Common in adults (18-60 years) and elderly (≥ 61 years)
[3] Reported as Very common only in paediatric subjects 6 months-8 years. Reported as Common in adolescents and adults 9-60 years of age and Uncommon in eldery (≥ 61 years)

The majority of these reactions usually disappear within 3 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.

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 to 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).
Post-marketing surveillance

No post-marketing experience exists for Foclivia.

In addition to the adverse events listed from clinical studies, the following adverse events were reported from post-marketing surveillance with H1N1v Focetria vaccine (licensed for use from 6 months of age during the 2009 influenza pandemic, and containing the same MF59 adjuvant and manufactured with the same process as Foclivia).

Blood and lymphatic system disorders
Lymphadenopathy.

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

Nervous system disorders
Dizziness, somnolence, syncope, presyncope, neuralgia, paraesthesia, convulsions and neuritis.

Cardiac disorders
Palpitation, tachycardia.

Respiratory, thoracic and mediastinal disorders
Cough.

Gastrointestinal disorders
Abdominal pain.

Skin and subcutaneous tissue disorders
Generalised skin reactions including pruritus, non-specific rash, angioedema.

Musculoskeletal and connective tissue 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 mm^3).

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 micrograms 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 micrograms 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 micrograms 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 2nd dose	Study V87P13 A/Vietnam/1194/2004 21 days after 2nd dose	Study V87P11 A/turkey/Turkey/1/2005 21 days after 2nd dose

	N=149	N=197	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 2nd dose N=69	Study V87P13 A/Vietnam/1194/2004 21 days after 2nd 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 mm^2

** Seroconversion was defined as an SRH area ≥25 mm^2 for subjects who were seronegative at baseline (Day 1 SRH area ≤4 mm^2) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area >4 mm^2)

*** 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 2nd dose N=84[a]	Study V87P13 A/Vietnam/1194/2004 21 days after 2nd dose N=210[b]	Study V87P11 A/turkey/Turkey/1/2005 21 days after 2nd 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 2nd dose N=66	Study V87P13 A/Vietnam/1194/2004 21 days after 2nd 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 mm^2

** Seroconversion was defined as an SRH area ≥25 mm^2 for subjects who were seronegative at baseline (Day 1 SRH area ≤4 mm^2) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area >4 mm^2)

*** 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 2nd dose	Study V87P2 Adults A/Vietnam/1194/2004 booster after 2nd dose	Study V87P1 Elderly A/Vietnam/1194/2004 booster after 2nd 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 mm^2

** Seroconversion was defined as an SRH area ≥25 mm^2 for subjects who were seronegative at baseline (Day 1 SRH area ≤4 mm^2) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area >4 mm^2)

*** 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 micrograms 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 micrograms 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 micrograms 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 micrograms 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 second 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 2nd dose N=70	Study V87P12 A/Vietnam/1194/ 2004 21 days after 2nd dose N=60	Study V87P3 A/Vietnam/1194/ 2004 21 days after 2nd dose N=30	Study V87P13 A/Vietnam/1194/ 2004 21 days after 2nd 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 mm^2

** Seroconversion was defined as an SRH area ≥25 mm^2 for subjects who were seronegative at baseline (Day 1 SRH area ≤4 mm^2) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area >4 mm^2)

*** 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 second 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 2nd dose N=37	Study V87P13 A/Vietnam/1194/2004 21 days after 2nd 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 mm^2
** 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 second dose in adults (18-60 years) and elderly (≥ 61years), measured by SRH and HI assays were as follows:

Anti-HA antibody		V87P11 Adults (18-60 years) N=182		V87P11 Elderly (≥61-89 years)[a] N=132	
		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)

Anti-HA antibody		V87P11 Adults (18-60 years) N=182		V87P11 Elderly (≥61-89 years)[a] N=132	
		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 mm^2

** Seroconversion was defined as an SRH area ≥25 mm^2 for subjects who were seronegative at baseline (Day 1 SRH area ≤4 mm^2) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area >4 mm^2)

*** 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 6to 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 to 65 years primed 6 to 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 prepandemic 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 second 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 second 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 mm^2, seroconversion: SRH area ≥25 mm^2 for subjects with a baseline SRH area ≤4 mm^2 or a minimum 50% increase in SRH area for subjects with >4 mm^2.

** 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).

Paediatric population

The immunogenicity of aH5N1 in the paediatric population was assessed in Studies V87P6 and V87_30.

Study 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 micrograms were administered three weeks apart and a third dose 12 months following the first dose.
After 3 weeks from the second vaccination (day 43) all age groups (i.e. 6 to 35 months, 3 to 8 years and 9 to 17 years) achieved high levels of antibodies to A/Vietnam/1194/2004 as evaluated with SRH and HI assays as presented in table below.

		Children (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 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)
SRH		**N=133**	**N=91**	**N=90**
	Seroprotection rate (95% CI)° Day 43	100% (97-100)	100% (96-100)	100% (96-100)
	Seroconversion rate (95% CI)°° Day 43	98% (95-100)	100% (96-100)	99% (94-100)
	Seroconversion factor (95% CI)°°° Day 43 to Day 1	16 (14-18)	15 (13-17)	14 (12-16)

* Seroprotection defined as HI titre ≥ 1:40
** Seroconversion defined as non-detectable titre to ≥1:40, or 4-fold increase from a detectable Day 1 titre
*** Geometric mean ratios of HI
° Seroprotection: SRH area ≥25 mm^2
°° Seroconversion defined as an SRH area ≥25 mm^2 for subjects who were seronegative at baseline (Day 1 SRH area ≤4 mm^2) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area >4 mm^2)
°°° Geometric mean ratios of SRH

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).

Study V87_30 was a randomised, observer-blind, multicentre study to measure the immunogenicity of six formulations in terms of H5N1 A/turkey/Turkey/1/2005 and MF59 adjuvant ratio. In this study, 420 paediatric subjects 6 months to 8 years of age were divided into two age cohorts: 6 to 35 months of age (N=210) and 3 to 8 years of age (N=210).

The vaccine was administered in two separate injections given 3 weeks apart. Antibody levels against A/turkey/Turkey/1/2005 were measured by HI and MN assays three weeks after the second vaccination (Day 43). The immunological response for the the approved formulation (7.5 micrograms HA with 100% MF59 adjuvant, 0.5 ml dose) and the study formulation with half the antigen content (3.75 micrograms HA with 100% MF59 adjvant, 0.5 ml dose), are presented below.

Formulation		**7.5 micrograms HA/ 100% MF59 Adjuvant**		**3.75 micrograms HA/ 100% MF59 Adjuvant**	
Age groups		**6 to 35 months**	**3 to 8 years**	**6 to 35 months**	**3 to 8 years**
		N=31	**N=36**	**N=36**	**N=33**
HI	Seroprotection rate (95% CI) * Day 43	87% (70-96)	86% (71-95)	86% (71-95)	88% (72-97)
	Seroconversion rate (95% CI)** Day 43	87% (70-96)	86% (71-95)	86% (71-95)	88% (72-97)
	Seroconversion factor (95% CI)*** Day 43 to Day 1	24 (14-40)	22 (14-34)	31 (19-51)	20 (13-31)
MN	% with Titre ≥1:40 (95% CI) Day 43	100% (89-100)	100% (90-100)	100% (90-100)	100% (89-100)
	Seroconversion rate (95% CI)** Day 43	100% (89-100)	100% (90-100)	100% (90-100)	100% (89-100)
	Seroconversion factor (95% CI)*** Day 43 to Day 1	165 (117-231)	125 (92-171)	214 (156-294)	132 (95-182)

* Seroprotection defined as HI titre ≥ 1:40

** Seroconversion defined as non-detectable titre to ≥1:40, or 4-fold increase from a detectable Day 1 titre

*** Geometric mean titre ratios

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 micrograms doses of Focetria was evaluated in 70 children and adolescents (9 to 17 years), 60 children (3 to 8 years), 58 children (12 to 35 months) and 49 infants (6 to 11 months). CHMP immunogenicity criteria set for adults (18 to 60 years) were met both after the first and the second 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: 27 June 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 micrograms 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

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.

Foclivia may contain trace residues of egg and chicken proteins, ovalbumin, kanamycin sulphate, neomycin sulphate, formaldehyde, hydrocortisone 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
Individuals 6 months of age and older: administer two doses (0.5 ml each), at least 3 weeks apart.

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

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

Method of administration
The vaccine is administered by intramuscular injection, preferably in the anterolateral aspect of the thigh in infants or in the deltoid muscle region of the upper arm in older individuals.

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, hydrocortisone 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 administrating 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, hydrocortisone 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.

Immunocompromised individuals
Immunocompromised individuals, whether due to the use of immunosuppressive therapy, a genetic defect, HIV infection, or other causes, may have reduced immune response to active immunisation.

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.

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).

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.

Excipients with known effect
Sodium
This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium free’

Potassium
This vaccine contains potassium, less than 1 mmol (39 mg) per dose, that is to say essentially ‘potassium-free’.

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.

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 (see section 5.3). Male fertility has not been assessed in animals.

4.7 Effects on ability to drive and use machines

Foclivia has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarly affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of H5N1 vaccine combined with MF59C.1 adjuvant (7.5 or 15 micrograms haemagglutinin, HA) containing either the A/turkey/Turkey/1/2005 or the A/Vietnam/1194/2004 strain has been evaluated in nine clinical trials in healthy subjects involving 5055 adults, elderly and children. There were 4041 adult subjects 18 to 60 years of age and 540 elderly subjects 61 years of age

and above. In the paediatric population, there were 214 subjects 6 to 35 months of age, 167 subjects 3 to 8 years of age and 93 subjects 9 to 17 years of age.

The overall safety profile was similar across the adult, elderly and paediatric populations.

Clinical trials in 383 subjects receiving MF59C.1 adjuvanted vaccine with an H1N1, H5N3 or H9N2 strain showed a similar safety profile to the H5N1 trials.

Irrespective of antigen dose, antigen subtype or age group, most local and systemic adverse reactions after administration were of short duration, with onset close to the time of vaccination, and were mild or moderate in severity. Across all trials, there was a general trend towards decreased reports of local adverse reactions after the second vaccination compared with the first.

Tabulated list of adverse reactions

In adults 18 to 60 years, the most frequently reported (≥10%) adverse reactions were injection site pain (59%), myalgia (34%), headache (26%), injection site redness (24%), fatigue (24%), injection site induration (21%), injection site swelling (15%), chills (13%) and maliase (13%).

In elderly subjects (≥61 years), the most frequently reported (≥10%) adverse reactions were injection site pain (35%), myalgia (24%), injection site redness (17%), headache (16%), chills (12%), fatigue (10%) and malaise (10%).

In children and adolescents 3 to 17 years of age, the most frequently reported (≥10%) adverse reactions were injection site pain (95%), headache (61%), myalgia (60%), fatigue (41%), injection site redness (60%), injection site induration (34%), injection site swelling (34%), malaise (32%), nausea (25%), sweating (18%), chills (19%), diarrhoea (18%) and injection site ecchymosis (16%).

Ininfants and children 6 to 35 months of age, the most frequently reported (≥10%) adverse reactions were injection site redness (62%), irritability (57%), tenderness (55%), unusual crying (48%), sleepiness (45%), injection site induration (38%), injection site swelling (37%) change in eating habits (36%), diarrhoea (34%), fever (27%), injection site ecchymosis (19%), vomiting (10%), sweating, (10%) and unusual sweating (10%).

The solicited and unsolicited adverse reactions reported after any vaccination dose (i.e. first, second or booster) across subjects age, 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)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**
Immune system disorders				Anaphylaxis
Metabolism and nutrition disorders	Change in eating habits[1]	Loss of appetite		
Nervous system disorders	Headache			
Gastrointestinal disorders	Nausea[2], Diarrhoea[2], Vomiting[2]			

Skin and subcutaneous tissue disorders	Sweating[2], Unusual sweating[1]		Urticaria	
Musculoskeletal and connective tissue disorders	Myalgia	Arthralgia		
General disorders and administration site conditions	Injection site swelling, Injection site pain, Injection site tenderness[1], Injection site induration, Injection site redness, Injection site ecchymosis[2], Fatigue, Chills/Shivering, Malaise, Sleepiness[1], Irritability[1], Unusual crying[1], Fever[3]	Injection site hemorrhage		

[1] Reported only in paediatric subjects 6-35 months
[2] Reported as Common in adults (18-60 years) and elderly (≥ 61 years)
[3] Fever: Reported as Very common only in paediatric subjects 6 months-8 years. Reported as Common in adolescents and adults 9-60 years of age and Uncommon in eldery (≥ 61 years)

The majority of these reactions usually disappear within 3 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.

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 to 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).

Post-marketing surveillance

No post-marketing experience exists for Foclivia administration.

In addition to the adverse events listed from clinical studies, the following adverse events were reported from post-marketing surveillance with H1N1v (licensed for use from 6 months of age during the 2009 influenza pandemic, and containing the same MF59 adjuvant and manufactured with the same process as Foclivia).

Blood and lymphatic system disorders
Lymphadenopathy.

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

Nervous system disorders
Dizziness, somnolence, syncope, presyncope, neuralgia, paraesthesia, convulsions and neuritis.

Cardiac disorders
Palpitation, tachycardia.

Respiratory, thoracic and mediastinal disorders
Cough.

Gastrointestinal disorders
Abdominal pain.

Skin and subcutaneous tissue disorders
Generalised skin reactions including pruritus, non-specific rash, angioedema.

Musculoskeletal and connective tissue 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 mm^3).

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 micrograms 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 micrograms 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 micrograms 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 2nd dose N=149	Study V87P13 A/Vietnam/1194/2004 21 days after 2nd dose N=197	Study V87P11 A/turkey/Turkey/1/2005 21 days after 2nd 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 2nd dose N=69	Study V87P13 A/Vietnam/1194/2004 21 days after 2nd 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 mm^2

** Seroconversion was defined as an SRH area ≥25 mm^2 for subjects who were seronegative at baseline (Day 1 SRH area ≤4 mm^2) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area >4 mm^2)

*** 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 2nd dose N=84[a]	Study V87P13 A/Vietnam/1194/2004 21 days after 2nd dose N=210[b]	Study V87P11 A/turkey/Turkey/1/2005 21 days after 2nd 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 2nd dose N=66	Study V87P13 A/Vietnam/1194/2004 21 days after 2nd 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 mm^2

** Seroconversion was defined as an SRH area ≥25mm^2 for subjects who were seronegative at baseline (Day 1 SRH area ≤4mm^2) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area >4 mm^2)

*** 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 2nd dose	Study V87P2 Adults A/Vietnam/1194/ 2004 booster after 2nd dose	Study V87P1 Elderly A/Vietnam/1194/2004 booster after 2nd 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 mm^2

** Seroconversion was defined as an SRH area ≥25 mm^2 for subjects who were seronegative at baseline (Day 1 SRH area ≤4 mm^2) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area >4 mm^2)

*** 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 micrograms 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 micrograms 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 micrograms 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 micrograms 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 second 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 2nd dose N=70	Study V87P12 A/Vietnam/1194/2004 21 days after 2nd dose N=60	Study V87P3 A/Vietnam/1194/2004 21 days after 2nd dose N=30	Study V87P13 A/Vietnam/1194/2004 21 days after 2nd 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 mm^2

** Seroconversion was defined as an SRH area ≥25 mm^2 for subjects who were seronegative at baseline (Day 1 SRH area ≤4 mm^2) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area >4 mm^2)

*** 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 second 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 2nd dose N=37	Study V87P13 A/Vietnam/1194/2004 21 days after 2nd 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 mm^2
** 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 second dose in adults (18-60 years) and elderly (≥61years), measured by SRH and HI assays were as follows:

Anti-HA antibody		V87P11 Adults (18-60 years) N=182		V87P11 Elderly (≥61-89 years)[a] N=132	
		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)

Anti-HA antibody		V87P11 Adults (18-60 years) N=182		V87P11 Elderly (≥61-89 years)[a] N=132	
	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 mm^2

** Seroconversion was defined as an SRH area ≥25 mm^2 for subjects who were seronegative at baseline (Day 1 SRH area ≤4 mm^2) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area >4 mm^2)

*** 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 to 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 to 65 years primed 6 to 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 prepandemic 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 second 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 second 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 second 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 mm^2, seroconversion: SRH area ≥25 mm^2 for subjects with a baseline SRH area ≤4 mm^2 or a minimum 50% increase in SRH area for subjects with >4 mm^2.

** 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).

Paediatric populations

The immunogenicity of aH5N1 in the paediatric population was assessed in Studies V87P6 and V87_30.

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 micrograms were administered three weeks apart and a third dose 12 months following the first dose. After 3 weeks from the second vaccination (day 43) all age groups (i.e. 6 to 35 months, 3 to 8 years and 9 to 17 years) achieved high levels of antibodies to A/Vietnam/1194/2004 as evaluated with SRH and HI assays as presented in table below.

		Children (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 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)
SRH		**N=133**	**N=91**	**N=90**
	Seroprotection rate (95% CI) ° Day 43	100% (97-100)	100% (96-100)	100% (96-100)
	Seroconversion rate (95% CI) °° Day 43	98% (95-100)	100% (96-100)	99% (94-100)
	Seroconversion factor (95% CI) °°° Day 43 to Day 1	16 (14-18)	15 (13-17)	14 (12-16)

* Seroprotection defined as HI titre ≥ 1:40

** Seroconversion defined as non-detectable titre to ≥1:40, or 4-fold increase from a detectable Day 1 titre

*** Geometric mean ratios of HI

° Seroprotection: SRH area ≥25 mm^2

°° Seroconversion defined as an SRH area ≥25 mm^2 for subjects who were seronegative at baseline (Day 1 SRH area ≤4 mm^2) or a significant (at least 50%) increase in SRH area for subjects who were seropositive at baseline (Day 1 SRH area >4 mm^2)

°°° Geometric mean ratios of SRH

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).

Study V87_30 was a randomised, observer-blind, multicentre study to measure the immunogenicity of several formulations of H5N1 A/turkey/Turkey/1/2005 and MF59 adjuvant. In this study, 420 paediatric subjects 6 months to 8 years of age were divided into two age cohorts: 6 to 35 months of age (N=210) and 3 to 8 years of age (N=210).

The vaccine was administered in two separate injections given 3 weeks apart. Antibody levels against A/turkey/Turkey/1/2005 were measured by HI and MN assays three weeks after the second vaccination (Day 43). The immunological response for the approved formulation (7.5 micrograms HA with 100% MF59 adjuvant, 0.5 ml dose) and the study formulation with half the antigen content (3.75 micrograms HA with 100% MF59 adjvant, 0.5 ml dose), are presented below.

Formulation		**7.5 micrograms HA/ 100% MF59 Adjuvant**		**3.75 micrograms HA/ 100% MF59 Adjuvant**	
Age groups		**6 to 35 months**	**3 to 8 years**	**6 to 35 months**	**3 to 8 years**
		N=31	**N=36**	**N=36**	**N=33**
HI	Seroprotection rate (95% CI) * Day 43	87% (70-96)	86% (71-95)	86% (71-95)	88% (72-97)
	Seroconversion rate (95% CI)** Day 43	87% (70-96)	86% (71-95)	86% (71-95)	88% (72-97)
	Seroconversion factor (95% CI)*** Day 43 to Day 1	24 (14-40)	22 (14-34)	31 (19-51)	20 (13-31)
MN	% with Titre ≥1:40 (95% CI) Day 43	100% (89-100)	100% (90-100)	100% (90-100)	100% (89-100)
	Seroconversion rate (95% CI)** Day 43	100% (89-100)	100% (90-100)	100% (90-100)	100% (89-100)
	Seroconversion factor (95% CI)*** Day 43 to Day 1	165 (117-231)	125 (92-171)	214 (156-294)	132 (95-182)

* Seroprotection defined as HI titre ≥ 1:40

** Seroconversion defined as non-detectable titre to ≥1:40, or 4-fold increase from a detectable Day 1 titre

*** Geometric mean titre ratios

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 micrograms doses of Focetria was evaluated in 70 children and adolescents (9 to 17 years), 60 children (3 to 8 years), 58 children (12 to 35 months) and 49 infants (6 to 11 months). CHMP immunogenicity criteria set for adults (18 to 60 years) were met both after the first and the second 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: 27 June 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

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 adverse events of special interest (AESI). This should include data from ongoing studies, or actual use if applicable, of the pandemic preparedness strains.

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, an annual 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, 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 .

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 System Organ Class (SOC) 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	PTs “Brachial plexopathy”, “Mononeuritis”, “Neuritis”, “Neuralgic amyotrophy”, “Radiculitis brachial”
Convulsions	narrow SMQ “Generalised convulsive seizures following immunisation”
Encephalitis (encephalomyelitis)	narrow SMQ “Noninfectious encephalitis”
Vasculitis	narrow SMQ “Vasculitis”
Guillain-Barré Syndrome (GBS)	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	PTs “Facial paralysis”, “Facial paresis”, “Facial nerve disorder”, “Oculofacial paralysis”, “Bell’s palsy”
Immune thrombocytopenia	HLT Thrombocytopenias

4. Serious unlisted adverse reactions (SOC, 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 and PT, stratified according to type of report (medically confirmed or non-medically confirmed), for the period covered by the report and cumulatively.

6. All spontaneous adverse reactions (SOC, PTs) 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 SOC) and not number of cases.

- All tables will be based on generic and not product-specific data[1]. 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 Enhanced Safety Surveillance (ESS). 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

i) EU member states for the reporting period by batch number,
ii) EU member states cumulatively and
iii) 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 an ESS as identified in the RMP	Depending on and after implementation of vaccine when first pandemic will take place

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

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 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

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

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 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, hydrocortisone, 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 posibility 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.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you experience the following side effect – you may need urgent medical attention or hospitalisation:

- difficulty in breathing, dizziness, a weak and rapid pulse and skin rash which are symptoms of an anaphylactic reaction (a very severe allergic reaction)

The side effects listed below have occurred with Foclivia in clinical studies:

Very common (affects more than 1 user in 10):
- Pain/tenderness at the site of injection
- Hardening of the skin at the injection site
- Injection site redness
- Injection site swelling
- Bruising of the skin at the injection site*
- Aching muscles
- Headache
- Fatigue
- Generally feeling unwell
- Shivering
- Sweating*
- Nausea*
- Change in eating habits**
- Diarrhoea
- Vomiting
- Sweating and unusual sweating**
- Sleepiness**
- Iritability**
- Unusual crying**
- Fever***

**Reported as, Common, in adults and elderly*
*** Reported only in infants and young children 6-35 months of age*
****Reported as Very common only in children 6 months-8 years. Reported as Common in adolescents and adults 9-60 years of age and Uncommon in eldery (over 61 years)*

Common (affects 1 to 10 users in 100):
- Aching joints
- Injection site bleeding
- Loss of appetite

Uncommon (affects 1 to 10 users in 1000)
- Hives (Urticaria)

These side effects are usually mild and disappear within 3 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.

Other rare side effects observed after routine use
The additional side effects listed below have occurred in the days or weeks after vaccination with another vaccine called Focetria H1N1v similar to Foclivia and with the same adjuvant. These side effects may occur with Foclivia.

- Generalised skin reactions including
  - Itching
  - Rash or swelling of the skin and mucous membranes
  - Angioedema (abnormal swelling of the skin, usually around the eyes, lips, tongue, hands or feet, due to an allergic reaction).

- Disorders of the gut such as
  - Abdominal pain

- Dizziness, drowsiness.

- Neurological disorders such as
  - Severe stabbing or throbbing pain along one or more nerves
  - Tingling
  - Fits
  - Neuritis (inflammation of nerves)
  - Syncope or presyncope (fainting or feeling about to faint)

- 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.

In addition side effects listed below have occurred in the days or weeks after vaccination with adjuvanted and not-adjuvanted 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

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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 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

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 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, hydrocortisone, 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 posibility 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.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you experience the following side effect – you may need urgent medical attention or hospitalisation:

- difficulty in breathing, dizziness, a weak and rapid pulse and skin rash which are symptoms of an anaphylactic reaction (a very severe allergic reaction)

The side effects listed below have occurred with Foclivia in clinical studies:

Very common (affects more than 1 user in 10):
- Pain/tenderness at the site of injection
- Hardening of the skin at the injection site
- Injection site redness
- Injection site swelling
- Bruising of the skin at the injection site*
- Aching muscles
- Headache
- Fatigue
- Generally feeling unwell
- Shivering
- Sweating*
- Nausea*
- Change in eating habits**
- Diarrhoea
- Vomiting
- Sweating and unusual sweating**
- Sleepiness**
- Iritability**
- Unusual crying**
- Fever***

**Reported as, Common, in adults and elderly*
*** Reported only in infants and young children 6-35 months of age*
**** Reported as Very common only in children 6 months-8 years. Reported as Common in adolescents and adults 9-60 years of age and Uncommon in eldery (over 61 years)*

Common (affects 1 to 10 users in 100):
- Aching joints
- Injection site bleeding
- Loss of appetite

Uncommon (affects 1 to 10 users in 1000)
- Hives (Urticaria)

These side effects are usually mild and disappear within 3 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.

Other rare side effects observed after routine use
The additional side effects listed below have occurred in the days or weeks after vaccination with another vaccine called Focetria H1N1v similar to Foclivia and with the same adjuvant. These side effects may occur with Foclivia.

- Generalised skin reactions including
  - Itching
  -
  - Rash or swelling of the skin and mucous membranes
  - Angioedema (abnormal swelling of the skin, usually around the eyes, lips, tongue, hands or feet, due to an allergic reaction).

- Disorders of the gut such as
  - Abdominal pain

- Dizziness, drowsiness.

- Neurological disorders such as
  - Severe stabbing or throbbing pain along one or more nerves
  - Tingling
  - Fits
  - Neuritis (inflammation of nerves)
  - Syncope or presyncope (fainting or feeling about to faint)

- 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.

In addition, the side effects listed below have occurred in the days or weeks after vaccination with adjuvanted and not-adjuvanted 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.
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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.