ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AFLUNOV suspension for injection in pre-filled syringe.
Zoonotic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

A/turkey/Turkey/1/2005 (H5N1)-like strain (NIBRG-23) (clade 2.2.1) 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 per 0.5 ml
polysorbate 80	1.175 milligrams per 0.5 ml
sorbitan trioleate	1.175 milligrams per 0.5 ml
sodium citrate	0.66 milligrams per 0.5 ml
citric acid	0.04 milligrams per 0.5 ml

AFLUNOV may contain trace residues of egg and chicken proteins, ovalbumin, kanamycin, 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

Active immunisation against H5N1 subtype of Influenza A virus in individuals 6 months of age and above.

AFLUNOV should be used in accordance with official recommendations.

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).

There is limited experience in elderly over 70 years of age (see section 5.1).

In the event of an officially declared influenza pandemic due to A/H5N1 virus, individuals previously vaccinated with one or two doses of AFLUNOV that contained haemagglutinin (HA) antigen derived from a different clade of the same influenza subtype as the influenza pandemic strain may receive a single dose of AFLUNOV instead of two doses that are required in previously unvaccinated individuals (see section 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 (egg and chicken proteins, ovalbumin, kanamycin and neomycin sulphate, formaldehyde, hydrocortisone and cetyltrimethylammonium bromide) of this vaccine.

However, in a pandemic situation caused by the strain included in this vaccine, 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.

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 individuals with a known hypersensitivity to the active substance, to any of the excipients listed in section 6.1 and to residues (eggs and chicken proteins, ovalbumin, kanamycin and 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.

Immunisation should be postponed in patients with febrile illness untill 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 AFLUNOV using the subcutaneous route of administration. Therefore, healthcare providers need to assess the benefits and potential risks of administering the vaccine in individuals with thrombocytopenia or any bleeding disorder that would contraindicate intramuscular injection unless the potential benefit outweighs the risk of bleedings.

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 AFLUNOV with other H5N1 monovalent vaccines.

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

AFLUNOV 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 AFLUNOV 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 were obtained from women who became pregnant during the course of clinical trials with AFLUNOV or similar pandemic H1N1v 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 AFLUNOV) which contains the same amount of adjuvant MF59C.1 as AFLUNOV.

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.

Since AFLUNOV is expected not to be used in an emergency situation, its administration during pregnancy might be deferred as a precautionary approach.

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

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

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

4.7 Effects on ability to drive and use machines

Aflunov 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 operate machinery.

4.8 Undesirable effects

Summary of the safety profile

The safety of H5N1 vaccine combined with MF59C.1 adjuvant 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 and elderly (7.5 or 15 micrograms HA), and children (7.5 micrograms HA). There were 4041 adults subjects 18 to 60 years of age, 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.

Irrespective of antigen dose,-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 malaise (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 doses (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, Malaise, Chills/Shivering, 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 side effects 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 AFLUNOV 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 AFLUNOV 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 AFLUNOV.

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 AFLUNOV).

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.

Muscoskeletal 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

Clinical trials with AFLUNOV have been conducted with either the former A/Vietnam/1194/2004 (H5N1) (clade 1) or the current A/turkey/Turkey/1/2005 (H5NI) vaccine strain (clade 2.2.1).

Immune response to AFLUNOV A/Vietnam/1194/2004 (H5N1) and A/turkey/Turkey/1/2005 (H5NI)

Adults (18-60 years)
A phase II clinical trial (V87P1) was conducted with AFLUNOV (A/Vietnam/1194/2004) in 312 healthy adults. Two doses of AFLUNOV were administered three weeks apart to 156 healthy adults. Immunogenicity was assessed in 149 subjects.

In phase III clinical trial (V87P13) 2693 adult subjects were enrolled and 2566 received two doses of AFLUNOV (A/Vietnam/1194/2004) administered three weeks apart. Immunogenicity was assessed in a subset (n=197) of subjects.

In a third clinical trial (V87P11) 194 adult subjects were enrolled and received two doses of AFLUNOV (A/turkey/Turkey/1/2005) 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 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

MicroNeutralisation (MN) results against homologous A/Vietnam/1194/2004) 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 (A/Vietnam/1194/2004 and to 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 three 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 homologous 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 elderly subjects 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. Up to 50% (N=33) of the elderly subjects aged 62 to 88 years immunised with AFLUNOV in trial V87P1 were seroprotected at six months.

A third (booster) dose of AFLUNOV was administered 6 months onwards after the primary vaccination. 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 booster after 2nd dose	Study V87P2 Adults booster after 2nd dose	Study V87P1 Elderly 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

Cross reactivity data in adults

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

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 V87P12 21 days after 2nd dose N=60	Study V87P3 21 days after 2nd dose N=30	Study V87P13 21 days after 2nd dose N=197
SRH	Seroprotection rate (95%CI)*	65% (52-77)	90% (73-98)	59% (52-66)
	Seroconversion rate (95%CI)**	65% (52-77)	86% (68-96)	49% (42-56)
	Seroconversion factor(95%CI)***	4.51 (3.63-5.61)	7.67 (6.09-9.67)	2.37 (2.1-2.67)
		N=60	N=30	N=197
HI	Seroprotection rate (95%CI)°	28% (17-41)	24% (10-44)	23% (18-30)
	Seroconversion rate (95%CI)°	28% (17-41)	21% (8-40)	19% (14-25)
	Seroconversion factor (95%CI)°°	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

° measured by HI assay ≥ 40

°° GMRs of HI

MN results for the three clinical studies 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.

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)
		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 AFLUNOV (A/Vietnam/1194/2004) induced high and rapid serological response in subjects primed 6 to8 years previously with two doses of a different surrogate H5N vaccine, having same formulation as AFLUNOV but using the strain H5N3.

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 AFLUNOV (A/Vietnam/1194/2004). 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 AFLUNOV (A/Vietnam/1194/2004) dose, 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 rated 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 AFLUNOV (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 AFLUNOV 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 AFLUNOV 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 AFLUNOV (A/Vietnam/1194/2004) in 471 children from 6 months to 17 years of age. Two doses (7.5 micrograms HA with 100% MF59 adjuvant, 0.5 ml each) of AFLUNOV were administered three weeks apart and a third dose (7.5 micrograms HA with 100% MF59 adjuvant, 0.5 ml) 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 (6to 35 months)	**Children (3 to 8years)**	**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*** 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

Information from non-clinical studies
Efficacy against challenge with virus homologous and heterologous to vaccine strains was evaluated in the ferret model (Study 765-N106857). AFLUNOV (A/Vietnam/1194/2004 clade 1) and an AFLUNOV-like H5N1 vaccine (A/turkey/Turkey/1/2005 clade 2.2.1) were tested. Animals received

one or two doses of vaccine containing 3.75 or 7.5 micrograms of antigen, followed by intranasal challenge on Day 42 after the second vaccine dose with a lethal dose of A/Vietnam/1203/04 virus.

All animals receiving 2 doses of AFLUNOV were protected, and 94% of animals receiving a single dose of AFLUNOV were protected. 87% of animals challenged with virus heterologous to the vaccine strain after 2 doses of vaccine were protected, and a single dose of heterologous vaccine protected 56% of the animals.

In a similar study, intranasal challenge was delayed until approximately 4 months after the second dose of vaccine was administered (Study 780-N007104). In this study 100% of animals were protected against homologous challenge, and 81% of animals were protected against heterologous challenge. Vaccination protected animals from lethal challenge even when HI antibody titres were low or undetectable.

In Study 673-N106850, AFLUNOV containing 7.5 micrograms of antigen (A/Vietnam/1194/2004) was immunogenic, able to fully protect against mortality and to reduce virus shedding from nasal washes after a lethal homologous challenge. In Study CBI-PCS-008, AFLUNOV containing either 7.5 or 15 micrograms of antigen (A/Vietnam/1194/2004) was able to reduce the proportion of animals shedding virus as well as the amount of virus shedding after a non-lethal homologous challenge. Serological testing indicated both doses were immunogenic and induced cross-reactive antibodies against A/turkey/Turkey/1/2005 (Study VIV-PCS-001).

Efficacy against challenge with the heterologous virus A/Indonesia/5/2005 was also tested (Study 2810200). Ferrets received one or two doses of vaccine (A/Vietnam/1194/2004). Two doses of vaccine protected 92% of animals, and a single dose of vaccine protected 50% of animals against challenge with the A/Indonesia/5/2005 virus. Lung damage was reduced in vaccinated groups. Viral shedding and viral titres in lungs were also reduced, suggesting that vaccination may reduce the risk of viral transmission.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data obtained with AFLUNOV 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 trials, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

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 or 10 pre-filled syringes.

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 AFLUNOV is a milky-white suspension.

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

Any unused vaccine and 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/1/10/658/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 November 2010
Date of latest renewal: 17 July 2015

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

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER 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.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be taken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports (PSURs)**

The requirements for submission of PSURs 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.

PSUR submission when AFLUNOV is used during an influenza pandemic:

During a pandemic situation, the annual frequency of PSUR submission may not be adequate for the safety monitoring of a pandemic vaccine for which high levels of exposure are expected within a short period of time. Such situation requires rapid notification of safety information that may have the greatest implications for benefit-risk balance in a pandemic. Prompt analysis of cumulative safety information, in light of extent of exposure, will be crucial for regulatory decisions and protection of the population to be vaccinated.

In consequence, as soon as the pandemic is declared and the zoonotic vaccine is used, the Marketing Authorisation Holder (MAH) shall submit more frequent simplified PSURs with a periodicity defined in the Risk Management Plan (RMP).

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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARDBOARD BOX

1. NAME OF THE MEDICINAL PRODUCT

AFLUNOV suspension for injection in pre-filled syringe.
Zoonotic influenza vaccine (H5N1) (surface antigen, inativated, adjuvanted)

2. STATEMENT OF ACTIVE SUBSTANCE

One dose of 0.5 ml contains: Influenza virus surface antigens (haemagglutinin and neuraminidase), propagated in fertilised hens' eggs from healthy chicken flocks, of strain:

A/turkey/Turkey/1/2005 (H5N1)-like strain (NIBRG-23) (clade 2.2.1) 7.5 micrograms haemagglutinin

Adjuvant: MF59C.1 oil in water emulsion containing squalene, as the oil phase, stabilised with polysorbate 80, sorbitan trioleate, sodium citrate and 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 pre-filled syringe (0.5 ml)
10 pre-filled syringes (0.5 ml)

5. METHOD AND ROUTE 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

EU/1/10/658/001 1 prefilled syringe
EU/1/10/658/002 10 prefilled syringes

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 OF ADMINISTRATION

AFLUNOV injection
H5N1 Zoonotic influenza vaccine
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

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

B. PACKAGE LEAFLET

Package leaflet: information for the user

AFLUNOV suspension for injection in pre-filled syringe
Zoonotic 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 AFLUNOV is and what it is used for

AFLUNOV is a vaccine for use in individuals 6 months of age and older, intended to be given in the context of outbreaks of zoonotic influenza viruses (coming from birds) with pandemic potential to prevent flu caused by H5N1 viruses similar to the vaccine strain reported in section 6.

Zoonotic influenza viruses occasionally infect humans, and can cause disease ranging from mild upper respiratory infection (fever and cough) to rapid progression to severe pneumonia, acute respiratory distress syndrome, shock and even death. Human infections are primarily caused by contact with infected animals, but do not spread easily between people.

AFLUNOV is intended also to be given when there is anticipation of a possible pandemic due to the same or a similar strain.

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

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

2. What you need to know before you receive AFLUNOV

You should not receive AFLUNOV:

- if you have previously had a sudden life-threatening allergic reaction to any ingredient of AFLUNOV (listed in section 6) or to any of the substances that may be present in trace amounts as follows: egg and chicken protein, ovalbumin, formaldehyde, kanamycin and neomycin sulphate (antibiotics), hydrocortisone or cetyltrimethylammonium bromide (CTAB). Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue. However, in a pandemic situation, it may be appropriate for you to be vaccinated with AFLUNOV provided that appropriate medical treatment is immediately available in case of an allergic reaction.

Warnings and precautions

Talk to your doctor or nurse before having this vaccine

- if you have had any allergic reaction to any ingredient contained in the vaccine, to egg and chicken protein, ovalbumin, formaldehyde, kanamycin and neomycin sulphate (antibiotics), hydrocortisone or cetyltrimethylammonium bromide (CTAB) (see section 6. Further information);

- if you have a severe infection with fever (over 38°C). If this applies to you then your vaccination will usually be postponed until you are feeling better. A minor infection such as a cold should not be a problem, but your doctor or nurse should advise whether you could still be vaccinated with AFLUNOV;

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

- in the presence of immune deficiencies AFLUNOV may be administered but a protective immune response may not be elicited.

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

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

AFLUNOV 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 AFLUNOV

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.

Data obtained in adults showed that AFLUNOV can be given at the same time as non-adjuvanted seasonal influenza vaccines. There is no information on administration of AFLUNOV with non-influenza vaccines. If administration of AFLUNOV with other vaccines can not 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 receiving this vaccine. Your doctor needs to assess the benefits and potential risks of giving you the vaccine.

Driving and using machines

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

AFLUNOV contains sodium and potassium.

AFLUNOV contains less than 1 mmol sodium (23 mg) and less than 1 mmol of potassium (39 mg) per 0.5 ml dose, i.e. essentially sodium- and potassium-free.

3. How AFLUNOV is given

Your doctor or nurse will administer 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. The vaccine should never be given into a vein

Individuals 6 months of age and older:
One dose of 0.5 ml will be given. A second dose of 0.5 ml should be given after an interval of at least 3 weeks.

There is limited experience in elderly over 70 years of age.

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

If you have any further questions on the use of this medicinal product, ask your doctor or nurse.

4. Possible side effects

Like all medicines, AFLUNOV 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 AFLUNOV 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 AFLUNOV and with the same adjuvant. These side effects may occur with AFLUNOV.

- 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 AFLUNOV.

- 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 AFLUNOV

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

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

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

Do not throw 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 AFLUNOV contains

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

  A/turkey/Turkey/1/2005 (H5N1)-like strain (NIBRG-23) (clade 2.2.1) 7.5 micrograms**
  per 0.5 ml dose

  * propagated in fertilised hens' eggs from healthy chicken flocks
  ** expressed in microgram haemagglutinin.

- Adjuvant MF59C.1:

The vaccine contains per 0.5 ml 9.75 mg squalene, 1.175 mg polysorbate 80, 1.175 mg sorbitan trioleate, 0.66 mg sodium citrate and 0.04 mg 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 AFLUNOV looks like and contents of the pack

AFLUNOV is a suspension for injection in a pre-filled syringe.
The suspension is a milky-white liquid.
It is provided in a ready-to-use pre-filled syringe, containing a single dose of 0.5 ml for injection.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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

Manufacturer
Seqirus Netherlands B.V.
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Netherlands

This leaflet was last revised in {MM/YYYY}

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