

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

A/turkey/Turkey/1/05 (H5N1)-like strain (NIBRG-23) per 0.5 ml dose	7.5 micrograms**
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\* propagated in fertilised hens' eggs from healthy chicken flocks

\*\* expressed in microgram 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

Excipient with known effect:

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

AFLUNOV may contain trace residues of egg and chicken proteins, ovalbumin, kanamycin and neomycin sulphate, barium sulphate, formaldehyde, cetyltrimethylammonium bromide (CTAB) and 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.

This indication is based on immunogenicity data from healthy subjects from the age of 18 years onwards following administration of two doses of the vaccine containing A/turkey/Turkey/1/05 (H5N1)-like strain (see section 5.1).

AFLUNOV should be used in accordance with official recommendations.

### 4.2 Posology and method of administration

#### Posology:

Adults and elderly (18 years of age and above):

One dose of 0.5 ml at an elected date.

A second dose of 0.5 ml should be given after an interval of at least 3 weeks.

AFLUNOV has been evaluated in healthy adults (18-60 years of age) and healthy elderly (over 60 years of age) following a 1, 22 day primary vaccination schedule, and booster vaccination (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, persons 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:

The safety and efficacy of AFLUNOV in subjects under 18 years of age have not yet been established.

Currently available data in subjects aged 6 months to 18 years of age are described in section 5.1 but no recommendation on a posology can be made.

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

Method of administration

Immunisation should be carried out by intramuscular injection into the deltoid muscle.

### **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, barium sulphate, formaldehyde and cetyltrimethylammonium bromide (CTAB)) 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**

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

Very limited data in subjects with co-morbidities, including immunocompromised subjects are available for this H5N1 vaccine.

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.

Immunization shall be postponed in patients with febrile illness or acute infection.

The vaccine should under no circumstances be administered intravascularly or intradermally.

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

Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient. A protective immune response may not be elicited in all vaccinees (see section 5.1).

Some cross-protection was observed against related H5N1 virus variants in clinical trials (see section 5.1).

Since a second dose is recommended, it should be noted that there are no safety, immunogenicity or efficacy data to support interchangeability of 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

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Data obtained in adults showed that co-administration of adjuvanted H5N1 vaccine and seasonal (inactivated surface, non-adjuvanted) antigens did not lead to any interference neither for seasonal strains nor for H5N1 strain. Single Radial Haemolysis (SRH) antibody response against an homologous H5N1 Vietnam strain at day 43 reached all CHMP criteria for 3 seasonal strains and H5N1-strain. Co-administration was not associated with higher rates of local or systemic reactions compared to administration of AFLUNOV alone.

Therefore the data indicate that AFLUNOV may be co-administered with non-adjuvanted seasonal influenza vaccines (with injections made into opposite limbs).

There are no data on co-administration of AFLUNOV with other vaccines.

If co-administration with another vaccine is considered, immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

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

Following influenza vaccination, false positive serology test results may be obtained by the ELISA method for antibody to human immunodeficiency virus-1 (HIV-1), hepatitis C virus and, especially, human T-lymphotropic virus type 1 (HTLV-1). In such cases, the Western Blot method is negative. These transitory false positive results may be due to IgM production in response to the vaccine.

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy

Limited data was obtained from women who became pregnant during the course of clinical trials with AFLUNOV (H5N1) or H1N1v vaccines adjuvanted with MF59C.1.

It is estimated that more than 90,000 women have been vaccinated during pregnancy with Focetria H1N1v vaccine which contains the same amount of adjuvant MF59C.1 as AFLUNOV. However information on outcomes is currently limited. Preliminary data from spontaneously reported events and ongoing post-marketing studies (pregnancy registry and prospective interventional study) do not suggest direct or indirect harmful effects on influenza vaccines adjuvanted with MF59 with respect to pregnancy, fertility, embryonic/foetal development, parturition, or post natal development.

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

A study in rabbits did not indicate reproductive or developmental toxicity of AFLUNOV (see section 5.3).

## **4.7 Effects on ability to drive and use machines**

Some of the undesirable effects mentioned under section 4.8 may affect the ability to drive or operate machinery.

## **4.8 Undesirable effects**

### a. Summary of the safety profile

The incidence of adverse reactions has been evaluated in seven clinical trials in adults (18 years old and above) involving over 4,300 adults and elderly receiving AFLUNOV (at least 7.5 µg HA, adjuvanted). There were 3872 subjects 18-60 years of age, 365 subjects 61-70 years of age, and 89 subjects greater than 70 years of age.

Consistent with the data observed by trial for solicited reactions, there was a general trend towards decreased reports of local reactions after the second vaccination compared with the first injection. Irrespective of antigen dose, almost all systemic reactions were reported on the day of vaccination (day 1) or during the 3 days immediately following.

Data on safety of a booster dose of the current AFLUNOV formulation are limited to three trials (V87P1, V87P2 and V87P1E1) that included 116 adults and 56 elderly. No increase in reactions was reported when a booster dose is administered 6 months-18 months later, after the initial dosing series. A slight increase in reactions in adults was reported when a booster dose is administered 18 months after the initial dosing series. In the elderly, the reported reactions increased with the third booster dose only when compared with the second dose.

### b. List of adverse reactions

The adverse reaction rates reported after either vaccination dose (i.e. 1<sup>st</sup>, 2<sup>nd</sup> or booster) were similar and are listed according to the following frequency:

Very common ( $\geq 1/10$ )

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

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

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

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

### Nervous system disorders

Very common: headache

Rare: convulsions

### Skin and subcutaneous tissue disorders

Common: sweating

Uncommon: urticaria

Rare: eye swelling

Musculoskeletal, connective tissue and bone disorders

Very common: myalgia

Common: arthralgia

Gastrointestinal disorders

Common: nausea

General disorders and administration site conditions

Very common: injection site swelling, injection site pain, injection site induration, injection site redness, fatigue

Common: injection site ecchymosis, fever, malaise, shivering

Uncommon: influenza like illness

Rare: anaphylaxis

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

Post-marketing surveillance

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

c. Description of selected adverse reactions

The following additional adverse events were reported from post-marketing surveillance with Focetria H1N1v (licensed for use in children 6 months of age and above, adults and the elderly with a composition that is similar to AFLUNOV):

Blood and lymphatic system disorders

Lymphadenopathy.

Cardiac disorders

Palpitation, tachycardia.

General disorders and administration site conditions

Asthenia.

Musculoskeletal, connective tissue and bone disorders

Muscular weakness, pain in extremities.

Respiratory disorders

Cough.

Skin and subcutaneous tissue disorders

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

Gastrointestinal disorders

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

Nervous system disorders

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

Immune system disorders

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

The following additional adverse events were reported from post-marketing surveillance with seasonal non-adjuvanted trivalent vaccines in all age groups and a seasonal adjuvanted trivalent vaccine with a

composition similar to AFLUNOV (surface antigen, inactivated, adjuvanted with MF59C.1) that is licensed 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<sup>3</sup>).

Immune system disorders

Vasculitis with transient renal involvement and exudative erythema multiforme.

Nervous system disorders

Neurological disorders, such as encephalomyelitis, and Guillain Barré syndrome.

d. Paediatric population

The incidence of adverse reactions has been evaluated in one clinical trial (Study V87P6) in children (6 months to 17 years old): Regardless of age, reactogenicity was higher after the first dose than after the second vaccination. Reactogenicity after a third dose, administered 12 months following the first dose, was higher than after both first and second dose. The percentages of subjects reporting local reactions were higher in the older age groups, mainly due to the higher reports for pain. In toddlers erythema and tenderness were the most commonly reported solicited local reactions; irritability and unusual crying were the most commonly reported solicited systemic reactions. In children and adolescents pain was the most frequently reported solicited local reaction, and fatigue and headache were the most commonly reported solicited systemic reactions. Across all ages, low percentages of subjects reported fever.

	<b>Injection 1</b>	<b>Injection 2</b>	<b>Injection 3</b>
	<b>Aflunov</b>	<b>Aflunov</b>	<b>Aflunov</b>
<b>Toddlers (6-&lt;36 months)</b>	<b>N=145</b>	<b>N=138</b>	<b>N=124</b>
Any	76%	68%	80%
Local	47%	46%	60%
Systemic	59%	51%	54%
Fever ≥ 38°C (≥ 40°C)	0%	0%	0%
Any Other Adverse Event	54%	49%	35%
<b>Children (3-&lt;9 years)</b>	<b>N=96</b>	<b>N=93</b>	<b>N=85</b>
Any	72%	68%	79%
Local	66%	58%	74%
Systemic	32%	33%	45%
Fever ≥ 38°C (≥ 40°C)	4%	2%	6%
Any Other Adverse Event	36%	31%	19%
<b>Adolescents(9-&lt;18 years)</b>	<b>N=93</b>	<b>N=91</b>	<b>N=83</b>
Any	91%	82%	89%
Local	81%	70%	81%
Systemic	69%	52%	69%
Fever ≥ 38°C (≥ 40°C)	0%	1%	2%
Any Other Adverse Event	30%	27%	22%

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.

This section describes the clinical experience with AFLUNOV following a two-dose administration and booster.

#### Immune response to Homologous Strains [A/Vietnam/1194/2004 (H5N1) and A/turkey/Turkey/1/05 (H5N1)]

##### Adults (18-60 years)

A clinical trial (Study V87P1) was conducted with a H5N1 vaccine combined with MF59C.1 adjuvant in 312 healthy adults. Two doses of vaccine containing H5N1 (A/Vietnam/1194/2004; 7.5 µg HA/dose adjuvanted) were administered three weeks apart to 156 healthy adults. In another clinical trial (Study V87P13) 2693 adult subjects were enrolled and received two doses of vaccine containing H5N1 (A/Vietnam/1194/2004; 7.5 µg HA/dose adjuvanted) administered three weeks apart. Immunogenicity was assessed in a subset (n=197) of study population. In a third clinical trial (Study V87P11) 194 adult subjects were enrolled and received two doses of vaccine containing H5N1 (A/H5N1/turkey/Turkey/1/05; 7.5 µg HA/dose adjuvanted) administered three weeks apart. Immunogenicity was assessed in a subset (n=182) of the study population.

The seroprotection rate\*, seroconversion rate\* and the seroconversion factor\*\* for anti-HA antibody to H5N1 A/Vietnam/1194/2004 and to A/H5N1/turkey/Turkey/1/05 in the adults measured by SRH assay was as follows:

Anti-HA antibody (SRH)	Study V87P1 21 days after 2 <sup>nd</sup> dose N=149	Study V87P13 21 days after 2 <sup>nd</sup> dose N=197	Study V87P11 21 days after 2 <sup>nd</sup> 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 21 days after 2 <sup>nd</sup> dose N=69	Study V87P13 21 days after 2 <sup>nd</sup> dose N=128	-
Baseline Serostatus	< 4 mm <sup>2</sup>	≥ 4 mm <sup>2</sup>	-
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)	-

\* measured by SRH assay  $\geq 25$  mm<sup>2</sup>

\*\* geometric mean ratios (GMRs) of SRH

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 MicroNeutralisation (MN) assay is in line with results obtained with SRH.

In Study V87P11 MN results against homologous A/H5N1/turkey/Turkey/1/05 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 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.

In a phase 2 clinical trial (Study V87P3) adult subjects aged 18-65 years primed 6-8 years previously with 2 doses of MF59-adjuvanted H5N3 vaccine/A/Duck/Singapore/97 were administered 2 booster doses of AFLUNOV. SRH results after the first dose, that mimic prepandemic priming plus single heterologous booster dose, met all CHMP criteria.

#### Elderly (>60 years)

The seroprotection rate\*, seroconversion rate\* and the seroconversion factor\*\* for anti-HA antibody to H5N1 A/Vietnam/1194/2004 and to A/H5N1/turkey/Turkey/1/05 (Study V87P11) in subjects aged over 60 (limited number of subjects were above 70 years of age) measured by SRH assay assessed in three clinical studies were as follows:

Anti-HA antibody (SRH)	Study V87P1 21 days after 2 <sup>nd</sup> dose N=84	Study V87P13 21 days after 2 <sup>nd</sup> dose N=210	Study V87P11 21 days after 2 <sup>nd</sup> dose N=132
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 21 days after 2 <sup>nd</sup> dose N=66	Study V87P13 21 days after 2 <sup>nd</sup> dose N=143
Baseline Serostatus	< 4 mm <sup>2</sup>	≥ 4 mm <sup>2</sup>
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)

\* measured by SRH assay ≥ 25 mm<sup>2</sup>

\*\* GMRs of SRH

MN results against homologous A/Vietnam/1194/2004 indicate a seroprotection and seroconversion rate ranging from of 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/H5N1/turkey/Turkey/1/05 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 1/5th of their post-vaccination level at day 202 as compared to day 43 after completion of primary schedules as assessed by Hemagglutination Inhibition (HI), SRH, and MN tests. Up to 50% of the elderly subjects immunised with AFLUNOV 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 2 <sup>nd</sup> dose N=71	Study V87P2 Adults booster after 2 <sup>nd</sup> dose N=13	Study V87P1 Elderly booster after 2 <sup>nd</sup> dose N=38
SRH			

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)

\* measured by SRH assay  $\geq 25 \text{ mm}^2$

\*\* GMRs of SRH

There is limited experience in the elderly

- Supportive data in adults

a) Cross reactivity

*Cross-reactive immune response elicited by A/H5N1/Vietnam/1194/2004 against A/H5N1/turkey/Turkey/1/05 and A/H5N1/Indonesia/5/05*

Some heterologous immune response against A/H5N1/turkey/Turkey/1/05 (NIBRG23; clade2.2) and A/H5N1/Indonesia/5/05 (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/1/05 after the 2<sup>nd</sup> 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 2 <sup>nd</sup> dose N=60	Study V87P3 21 days after 2 <sup>nd</sup> dose N=30	Study V87P13 21 days after 2 <sup>nd</sup> 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) <sup>o</sup>	28% (17-41)	24% (10-44)	23% (18-30)
	Seroconversion rate (95% CI) <sup>o</sup>	28% (17-41)	21% (8-40)	19% (14-25)
	Seroconversion factor (95% CI) <sup>oo</sup>	2.3 (1.67-3.16)	1.98 (1.22-3.21)	1.92 (1.64-2.25)

\* measured by SRH assay  $\geq 25 \text{ mm}^2$

\*\* GMRs of SRH

<sup>o</sup> measured by HI assay  $\geq 40$

<sup>oo</sup> 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/05 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/05 ranging from 1.59 to 2.95.

*Cross-reactive immune response elicited by A/H5N1/turkey/Turkey/1/05 against A/H5N1/Indonesia/5/05 and A/H5N1/Vietnam/1194/2004*

Heterologous immune response against A/H5N1/Indonesia/5/05 (clade 2.1) was detectable in study V87P11 after the second vaccination, indicating cross-reactivity of the clade 2.2 vaccine against clade 2.1 strains.

Seroprotection rate\*, seroconversion rate\* and the seroconversion factor\*\* for anti-HA antibodies to A/H5N1/Indonesia/5/05 and A/H5N1/Vietnam/1194/2004 after the 2<sup>nd</sup> dose in adults (18-60 years) and elderly (>60 years), measured by SRH and HI assays were as follows:

Anti-HA antibody		V87P11 Adults (18-60 years) N=186		V87P11 Elderly (>60 years) N=142	
		A/Indonesia/ 5/05	A/Vietnam/ 1194/2004	A/Indonesia/ 5/05	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)

\* measured by SRH assay  $\geq 25 \text{ mm}^2$

\*\* GMRs of SRH

° measured by HI assay  $\geq 40$

°° GMRs of HI

MN results for A/H5N1/Indonesia/5/05 revealed a seroprotection rate of 38% (31-45) in adults (18-60 years) and 14% (8-20) in elderly (>60 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/H5N1/Vietnam/1194/2004 revealed a seroprotection rate of 10% (6-16) in adults (18-60 years) and 6% (3-11) in elderly (>60 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.

b) Long term booster immune memory

A single vaccination with AFLUNOV (H5N1, A/Vietnam/1194/2004) induced high and rapid serological response in subjects primed 6-8 years previously with two doses of a different surrogate H5N vaccine, having same formulation as AFLUNOV but using the strain H5N3.

c) Trial on different vaccination schedules:

In a clinical trial evaluating 4 different vaccination schedules in 240 subjects 18 to 60 years of age, where the second dose was after either 1, 2, 3 or 6 weeks after the first AFLUNOV dose, SRH CHMP criteria were achieved in all the vaccine schedule groups after 3 weeks from the 2<sup>nd</sup> vaccination. The magnitude of immune response was lower in the group who received the 2<sup>nd</sup> dose 1 week later and higher in the groups with longer interval schedules.

• Available data in paediatric populations

A clinical trial (Study V87P6) was conducted with a H5N1 vaccine combined with MF59C.1 adjuvant in 471 children from 6 months to 17 years of age. Two doses of AFLUNOV were administered three

weeks apart and a third dose 12 months following the first dose. After 3 weeks from the 2<sup>nd</sup> vaccination (day 43) all age groups (i.e. 6-35 months, 3-8 years and 9-17 years) achieved high levels of antibodies to (A/Vietnam/1194/2004) as evaluated with SRH and HI assays as presented in table below\*. In this trial no vaccine related SAEs were observed.

		<b>Toddlers (6-&lt;36 months)</b>	<b>Children (3-&lt;9 years)</b>	<b>Adolescents (9-&lt;18 years)</b>
		<b>N=134</b>	<b>N=91</b>	<b>N=89</b>
HI	% SP (95% CI) Day 43	97% (92-99)	97% (91-99)	89% (80-94)
	GMR Day 43 to Day 1	129 (109-151)	117 (97-142)	67 (51-88)
	% SC (95% CI) Day 43	97% (92-99)	97% (91-99)	89% (80-94)
SRH		<b>N=133</b>	<b>N=91</b>	<b>N=90</b>
	% SP (95% CI) Day 43	100% (97-100)	100% (96-100)	100% (96-100)
	GMR (95% CI) Day 43 to Day 1	16 (14-18)	15 (13-17)	14 (12-16)
	% SC (95% CI) Day 43	98% (95-100)	100% (96-100)	99% (94-100)

\* In the absence of CHMP immunogenicity criteria for children, the CHMP immunogenicity criteria used to evaluate seasonal flu vaccines in adults were applied to the serological data obtained after vaccination of children.

SP= seroprotection

SC= seroconversion

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).

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

#### Information from non-clinical trials

Efficacy against challenge with virus homologous and heterologous to vaccine strains was evaluated in the ferret model. AFLUNOV, containing HA from A/Vietnam/1194/2004 (homologous to the challenge strain) and an AFLUNOV-like H5N1 vaccine, containing hemagglutinin from the A/turkey/Turkey/1/2005-like (heterologous to the challenge strain) were tested. Groups of 8 ferrets received one (day 21) or two (days 0 and 21) doses of vaccine containing 3.75 or 7.5 micrograms of antigen. Control animals received adjuvant alone. Animals were challenged by the intranasal route on day 42 with a lethal dose of A/Vietnam/1203/04 virus. Animals were monitored for 16-17 days after challenge to allow for a comprehensive assessment of disease progression, including the time of onset of symptoms, mortality, or subsequent recovery.

All (100%) 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. All control animals died within 7 days of challenge. Vaccination protected animals from lethal challenge with virus homologous and heterologous to the vaccine.

In a similar study, intranasal challenge was delayed until approximately 4 months after the second dose of vaccine containing either 3.75 or 7.5 micrograms of antigen was administered. 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 titers were low or undetectable.

Efficacy against challenge with the heterologous virus A/Indonesia/5/05 was also tested. Groups of 6 ferrets received one dose of vaccine (day 21) containing 3.75 micrograms of antigen or two doses of vaccine (days 0 and 21) containing either 1.0 or 3.75 micrograms of antigen (A/Vietnam/1194/2004). A lethal challenge was administered by the intratracheal route on day 49. Two doses of vaccine protected 92% of animals, and a single dose of vaccine protected 50% of animals against the A/Indonesia/5/05 virus. Compared to the adjuvant control group, lung damage was reduced in vaccinated groups. Viral shedding and viral titers 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 (E508),  
Potassium dihydrogen phosphate (E340),  
Disodium phosphate dihydrate (E339),  
Magnesium chloride hexahydrate (E511),  
Calcium chloride dihydrate (E509),  
Sodium citrate (E311),  
Citric acid (E330),  
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.  
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**

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

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

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

#### **7. MARKETING AUTHORISATION HOLDER**

Seqirus S.r.l.  
Via Fiorentina, 1  
Siena, Italy.

#### **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/10/658/001-002

#### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

29 November 2010

#### **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

GSK Vaccines S.r.l.  
Via Fiorentina, 1 – 53100 Siena  
Italy

GSK Vaccines S.r.l.  
Loc. Bellaria – 53018 Rosia – Sovicille (SI)  
Italy

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

Name and address of the manufacturer responsible for batch release

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

**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)

PSUR submission when AFLUNOV is used during an influenza pandemic:

During a pandemic situation, the frequency of submission of periodic safety update reports specified in Article 24 of Regulation 726/2004/EC will not be adequate for the safety monitoring of a pandemic vaccine for which high levels of exposure are expected within a short period of time. Such situation requires rapid notification of safety information that may have the greatest implications for risk-benefit 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 addition, duration a pandemic, resources needed for an in-depth evaluation of PSURs in the format as defined in Volume 9a of the Rules Governing Medicinal Product in the European Union may not be adequate for a rapid identification of a new safety issue.

In consequence, as soon as the pandemic is declared and the prepandemic vaccine is used, the Marketing Authorisation Holder (MAH) shall submit more frequent simplified periodic safety update reports with a format and a periodicity defined in the “CHMP Recommendations for the Core Risk Management Plan for Influenza Vaccines prepared from viruses with the potential to cause a pandemic

and intended for use outside of the core dossier context” (EMEA/49993/2008), and any subsequent update.

**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.  
Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, 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/1/05 (H5N1)-like strain (NIBRG-23)                      7.5 micrograms haemagglutinin

**Adjuvant:** MF59C.1 oil composed of squalene, polysorbate 80 and sorbitan trioleate.

#### **3. LIST OF EXCIPIENTS**

Sodium chloride  
Potassium chloride (E508)  
Potassium dihydrogen phosphate (E340)  
Disodium phosphate dihydrate (E339)  
Magnesium chloride hexahydrate (E511)  
Calcium chloride dihydrate (E 509)  
Sodium citrate (E311)  
Citric acid (E330)  
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.

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

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE 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 Fiorentina, 1  
Siena, 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

**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 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**

Prepandemic 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
2. What you need to know before you receive AFLUNOV
3. How AFLUNOV is given
4. Possible side effects
5. How to store AFLUNOV
6. Contents of the pack and other information

#### **1. What AFLUNOV is and what it is used for**

AFLUNOV is a vaccine for use in adults (from 18 to 60 years old). and elderly (over 60 years old).

It is intended to be given before or during the next pandemic influenza (flu) to prevent flu caused by the H5N1 type of the virus.

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

When a person is given the vaccine, the immune system (the body's natural defense 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, barium sulphate, formaldehyde, kanamycin and neomycin sulphate (antibiotics) or cetyltrimethylammonium bromide (CTAB). Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue. However, in a pandemic situation, it may be appropriate for you to 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 other than a sudden life-threatening allergic reaction to any ingredient contained in the vaccine, to egg and, chicken protein, ovalbumin, formaldehyde, kanamycin and neomycin sulphate (antibiotics) or cetyltrimethylammonium bromide (CTAB) (see section 6. Further information);
- if you have a severe infection with a high temperature (over 38°C). If this applies to you then your vaccination will usually be postponed until you are feeling better. A minor infection such as a cold should not be a problem, but your doctor or nurse should advise whether you could still be vaccinated with 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.

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. The vaccine will be injected into the muscles of the upper arm (deltoid muscle). The vaccine should never be given into a vein.

#### Adults (from 18 to 60 years old) and elderly (over 60 years old):

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.

#### **Use in children**

Children from 6 months to 17 years of age

There is limited experience in children between 6 months and 17 years of age. Vaccination is currently not recommended in this age group.

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.

Allergic reactions may occur following vaccination, in rare cases leading to shock. Doctors are aware of this possibility and have emergency treatment available for use in such cases.

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

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

- Pain
- Hardening of the skin at the injection site
- Injection site redness, injection site swelling
- Pain at the site of injection
- Aching muscles
- Headache
- Sweating
- Fatigue.

#### Common (affects 1 to 10 users in 100):

- Bruising of the skin at the injection site
- Fever and nausea
- Generally feeling unwell
- Shivering.

#### Uncommon (affects 1 to 10 users in 1.000):

- Flu like symptoms.

Rare (affects 1 to 10 users in 10.000):

- Convulsions
- Eye swelling
- Anaphylaxis.

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

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

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

Other rare side effects observed after routine use:

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

- Generalised skin reactions including
  - Itching
  - Urticaria (hives)
  - Rash or swelling of the skin and mucous membranes.
- Disorders of the gut such as
  - Nausea
  - Vomiting
  - Abdominal pain
  - Diarrhoea
- Headache, dizziness, drowsiness, fainting.
- Neurological disorders such as
  - Severe stabbing or throbbing pain along one or more nerves
  - Tingling
  - Fits
  - Neuritis (inflammation of nerves)
- Swollen lymph nodes, palpitations, weakness, pain in the extremities and cough.
- Allergic reactions possibly with shortness of breath, wheezing, swelling of the throat, or leading to a dangerous decrease of blood pressure, which, if untreated, may lead to shock. Doctors are aware of this possibility and have emergency treatment available for use in such cases.

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

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

### **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/1/05 (H5N1)-like strain (NIBRG-14) 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 and 1.175 mg sorbitan trioleate.
- Other ingredients:  
The other ingredients are: sodium chloride, potassium chloride, potassium dihydrogen phosphate, disodium phosphate dihydrate, magnesium chloride hexahydrate, calcium chloride dihydrate, sodium citrate, citric acid and water for injections.

### **What 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 Fiorentina, 1  
Siena, Italy.

### Manufacturer

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

<b>België/Belgique/Belgien; Luxembourg/Luxemburg; Nederland; България; Danmark; Ελλάδα; Ísland; Italia; Norge; Eesti; Latvija; Lietuva; Ireland; Κύπρος; Hrvatska; Malta; România; Slovenija; Suomi; Finland; Sverige</b> Seqirus S.r.l Tél/Tel: +39 800 456929; +39 0577 539999	
<b>Česká republika</b> Novartis s.r.o. Tel: +420 225 775 111	<b>Österreich</b> Novartis Pharma GmbH Tel: +43 1 86 6570
<b>Deutschland</b> Seqirus GmbH Tel: +49 (800) 26201090	<b>Polska</b> Novartis Poland Sp. z. o. o. Tel: +48 22 550 8888
<b>España</b> Novartis Farmacéutica, S.A. Tel: +34 93 306 4200	<b>Portugal</b> Novartis Farma - Produtos Farmacêuticos, S.A. Tel: +351 21 000 8600
<b>France</b> Novartis Pharma SAS Tél: + 33 1 55 47 66 00	<b>Slovenská republika</b> Novartis Slovakia s.r.o. Tel: + 42 022 5775 111
<b>Magyarország</b> Novartis Hungária Kft. Tel.: + 36 1 457 6500	<b>United Kingdom</b> Seqirus Vaccines Limited Tel: +44 (0) 151 705 5445

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>.