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/1/2005 (H5N1)-like strain used (NIBRG-23) 7.5 micrograms** per 0.5 mL dose

* propagated in eggs
** expressed in micrograms of haemagglutinin.

Adjuvant MF59C.1 containing:

squalene	9.75 milligrams
polysorbate 80	1.175 milligrams
sodium citrate dihydrate	0.66 milligrams
citric acid monohydrate	0.04 milligrams
sorbitan trioleate	1.175 milligrams

For a 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/1/2005 (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):
Individuals 18 years and older: Two 0.5 mL doses administered with an interval of at least 21 days.between doses.

In the event of an officially declared influenza pandemic due to H5N1 virus, persons previously vaccinated with one or two doses of AFLUNOV® that contained HA antigen derived from a different clade of the same influenza subtype as the pandemic influenza strain may receive a single dose of adjuvanted H5N1 pandemic vaccine instead of two doses that are required in previously unvaccinated individuals (see section 5.1).

Paediatric population:
There is limited experience in children between 6 months and 17 years of age (see section 5.1).

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 (ovalbumin from eggs, kanamycin and neomycin sulphate, formaldehyde, cetyltrimethylammonium bromide (CTAB) and hydrocortisone) 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 administrating this vaccine to persons with a known hypersensitivity to the active substance, to any of the excipients and to residues (ovalbumin from eggs, kanamycin and neomycin sulphate, formaldehyde,cetyltrimethylammonium bromide (CTAB) and hydrocortisone).

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 until the fever is resolved.

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

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 in the immune responses against the seasonal strains or H5N1 strains.
Co-administration was not associated with higher rates of local or systemic reactions compared to administration of AFLUNOV® alone.

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, other than non-adjuvanted seasonal influenza vaccines.
If co-administration with another vaccine is considered, immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

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

4.6 Fertility, pregnancy and lactation

A reproductive and developmental toxicity study was performed with AFLUNOV® in female rabbits at a dose approximately 15 times the human dose (based on body weights). There was no evidence of maternal, foetal, or postnatal developmental effects due to AFLUNOV®.
Limited data was obtained from women who became pregnant during the course of clinical trials with AFLUNOV® (H5N1) or similar H1N1v vaccines adjuvanted with MF59C.1.

However, it is estimated that during the 2009 H1N1 pandemic more than 90,000 women have been vaccinated during pregnancy with H1N1v vaccine FOCETRIA® which contains the same amount of adjuvant MF59C.1 as AFLUNOV®.

Postmarketing spontaneously reported adverse events 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.

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

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.

There were no effects on the mating performance or fertility of female rabbits in an embryofoetal and developmental toxicity study in which rabbits were intramuscularly injected with AFLUNOV® 35, 20, and 6 days prior to mating and on gestation days 7 and 20. Male fertility has not been assessed in animals. (See section 5.3)

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse reactions from clinical trials in 18 years old and above

The incidence of adverse reactions has been evaluated in seven clinical trials in healthy subjects involving approximately 4326 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 third dose is administered 6 months-1 year or later after the initial dosing series. A slight increase in reactions in adults was reported when a booster dose was administered 18 months after the initial dosing series.

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

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)

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

Immune system disorders
Rare: anaphylaxis

Nervous system disorders
Very common: headache

Gastrointestinal disorders

Common: nausea

Skin and subcutaneous tissue disorders
Common: sweating

Musculoskeletal and connective tissue disorders
Very common: myalgia
Common: arthralgia

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

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

Clinical trials in special populations

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

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 through 60 years of age, slightly higher rates of nausea (13.0%) were reported. In addition, higher rates of arthralgia (up to 23.3%) were reported in both adult and elderly subjects, who were immunocompromised or with underlying medical conditions.

The following solicited adverse reactions were additionally collected in these two studies and reported with the following frequencies across subjects who received 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%). Higher frequencies of diarrhoea, loss of appetite and vomiting were reported by subjects with underlying medical conditions 18 through 60 years of age and by subjects with immunosuppressive conditions irrespective of age as compared to healthy subjects.

Adverse reactions from clinical trial in children aged 6 months to 17 years (Study V87P6)

Regardless of age, reactogencity 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.

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

Postmarketing surveillance

No postmarketing surveillance data are available following AFLUNOV® administration.

In addition to the adverse events reported from clinical studies, the following adverse events were reported from postmarketing surveillance with Focetria H1N1v (licensed for use from 6 months of age during the 2009 influenza pandemic and containing the same MF59® adjuvant and manufactured with the same process as AFLUNOV®):

Blood and lymphatic system disorders
Lymphadenopathy.

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

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

Cardiac disorders
Palpitation, tachycardia.

Respiratory, thoracic and mediastinal disorders
Cough.

Gastrointestinal disorders
Abdominal pain.

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

Musculoskeletal and connective tissue disorders
Muscular weakness, pain in extremities.

General disorders and administration site conditions
Asthenia.

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

Immune response to AFLUNOV® [A/Vietnam/1194/2004 (H5N1) and A/H5N1/turkey/Turkey/1/05 (H5N1)]:

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 a 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/H5N1/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 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	87% (77-94)	73% (65-81)

(95%CI)**		
Seroconversion factor (95%CI)***	8.87 (7.09-11)	2.71 (2.38-3.08)

* Seroprotection SRH ≥ 25 mm^2
** Seroconversion was defined as an SRH area ≥ 25 mm^2 for subjects who were seronegative at baseline (Day1 SRH area ≤ 4 mm^2) or a significant (at least 50%) increase in SRH area for subjects who were seroprotective at baseline (Day 1 SRH area > 4 mm^2)
*** Geometric mean ratios of SRH

Microneutralisation (MN) results against 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 (≥ 61years)

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 (V87P11)) in subjects 61 years of age and older (limited number of subjects were above 70 years of age, N=123) measured by SRH assay assessed in two clinical studies were as follows:

Anti-HA antibody (SRH)	Study V87P1 A/Vietnam/1194/2004 21 days after 2nd dose N=84	Study V87P13 A/Vietnam,/1194/2004 21 days after 2nd dose N=210	Study V87P11 A/turkey/Turkey/1/2005 21 days after 2nd 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 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)

*Seroprotection SRH ≥ 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 > 4mm^2
*** Geometric mean ratios of SRH

MN results against homologous A/Vietnam/1194/2004 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.

Based on data obtained from trials V87P1, V8711 and V87_13, persistence of antibodies after primary vaccination in elderly subjects, 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 HI, SRH, and MN tests. Up to 50% (N=33) of the elderly subjects immunised with AFLUNOV® in trial V87P1were 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 2rd 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	83% (72-91)	69% (39-91)	63% (46-78)

rate (95%CI)**			
Seroconversion factor (95%CI)***	5.96 (4.72-7.53)	2.49 (1.56-3.98)	5.15 (3.46-7.66)

*Seroprotection SRH ≥ 25 mm^2
** Seroconversion was defined as an SRH area ≥ 25mm^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 seroprotective at baseline (Day 1 SRH area > 4 mm^2)
*** Geometric mean ratios of SRH

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

Cross reactivity data in adults

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

Some heterologous immune response against A/turkey/Turkey/2005 (NIBRG23; clade 2.2.1) and A/Indonesia/5/2005 (clade 2.1) was detectable both after the second and third vaccinations with A/Vietnam/1194/2004, 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/2005 after the 2nd dose in adults 18-60 years of age, measured by SRH and HI assays were as follows:

	Anti-HA antibody	Study 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 ≥ 25 mm^2
** Seroconversion was defined as SRH area ≥ 25mm^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
° Measured by HI assay ≥ 40
°° Geometric mean ratios 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 Geometric Mean Ratio (GMR) against A/turkey/Turkey/2005 ranging from 1.59 to 2.95.

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

Heterologous immune response against A/Indonesia/5/2005 (clade 2.1) and A/Vietnam/1194/2004 (clade 1) was detectable in study V87P11 after the second vaccination with A/turkey/Turkey/1/2005, indicating cross-reactivity of the clade 2.2.1 vaccine against clade 1 and 2.1 strains.

Seroprotection rate, seroconversion rate and the seroconversion factor for anti-HA antibodies to A/ Indonesia/5/05 (clade 2.1) and A/ Vietnam/1194/2004 after the 2nd dose in adults 18 60 years of age, measured by SRH and HI assays in adults and elderly were as follows:

Anti-HA antibody		V87P11 Adults N=182		V87P11 Elderly 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)

* 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 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.

In the same study heterologous immune response against A/H5N1/Vietnam/1194/2004 was lower. MN results 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.

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.

In a phase 1 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.

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 was after 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 2nd vaccination achieved high levels of antibodies as evaluated with SRH. SRH seroprotection rates ranged from 86% to 98%, seroconversion rates from 64% to 90%, and GMR ranged from 2.92 to 4.57. The magnitude of immune response was lower in the group who received the 2nd dose 1 week later and higher in the groups with longer interval schedules.

Subjects with underlying medical or immunosuppressive conditions:

Immunogenicity of AFLUNOV® (A/turkey/Turkey/1/2005) in adults (18-60) and elderly (≥61 years) subjects with underlying medical conditions (V87_25) or immunosuppressive conditions (V87_26) in comparison to healthy adults (18-60) 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 these trials, AFLUNOV® was shown to be immunogenic by inducing an increase in antibody titres (HI, SRH and MN) following both a single and second vaccination with AFLUNOV®, however, in both studies the immune response was lower in subjects with underlying medical or immunosuppressive conditions compared with healthy subjects. Although an increase in immune response was seen at day 22 following a single vaccination, the data support the administration of two doses.

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

Study V87_25				
	Adults (18- 60 years)	Adults (18-60 years)	Elderly (≥61 years)	Elderly (≥61 years)
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 (18- 60 years)	Adults (18- 60 years)	Elderly (≥61 years)	Elderly (≥61 years)
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)

* 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.

Supportive data in paediatric populations

A clinical trial (V87P6) was conducted with AFLUNOV® (A/Vietnam/1194/2004) 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 2nd vaccination (day 43) all age groups (i.e. 6-35 months, 3-8 years and 9-17 years) achieved high levels of antibodies to (A/Vietnam/1194/2004) as evaluated with SRH and HI assays as presented in table below*. In this trial no vaccine related SAEs were observed.

		Toddlers (6-<36 months)	**Children (3-<9 years)**	**Adolescents (9-<18 years)**
		N=134	**N=91**	**N=89**
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		**N=133**	**N=91**	**N=90**
	% 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.

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).

Information from non-clinical studies

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 and AFLUNOV® A/turkey/Turkey/1/2005 were tested. Animals received one or two doses of vaccine containing 3.75 or 7.5 micrograms of antigen, followed by challenge.

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. 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/5/2005 was also tested. 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 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 (FLUAD®) reveal no special hazard for humans based on animal studies that are appropriate for the safety assessment of vaccines. AFLUNOV® was immunogenic in mice and rabbits, and immunogenic and protective in ferrets. Studies with FLUAD® showed no evidence of systemic toxicity, demonstrated good local tolerability (repeat-dose toxicity in rabbits), and sensitization was not induced (Guinea pigs).

In a reproductive and developmental toxicity study, female rabbits received three intramuscular doses of AFLUNOV® before mating and two additional doses during gestation. On a body weight basis, each dose administered to rabbits was approximately 15 times the human dose. There were no maternal or teratogenic effects, or effects on fetal loss, mortality or resorption, reductions in body weight of fetuses, or other developmental abnormalities.

Genotoxicity and carcinogenic potential were not assessed because these studies are not appropriate for a vaccine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride,
Potassium chloride,
Potassium dihydrogen phosphate,
Disodium phosphate dihydrate,
Magnesium chloride hexahydrate,
Calcium chloride dihydrate,
Water for injections.

For the adjuvant, see section 2.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

24 months

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.
AFLUNOV® must be kept out of the reach and sight of children.

6.5 Nature and contents of container

0.5 mL in pre-filled syringe (type I glass) with plunger-stopper (bromo-butyl rubber) and with attached needle (1 inch, 25 mm). Packs of 1 or 10.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Gently shake before use.
After shaking, the normal appearance of 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 compliance with local requirements.

7. PRODUCT REGISTRANT

Seqirus Pte Ltd
#05-02 Marina Bay Financial Centre
8 Marina Boulevard,
Singapore 018981

8. DATE OF REVISION OF THE TEXT

March 2022