

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics 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/Vietnam/1194/2004 (H5N1)-like strain (NIBRG-14) 7.5 micrograms** per 0.5 ml dose

* propagated in eggs

** 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

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/Vietnam/1194/2004 (H5N1)-like strain (see section 5.1).

Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics 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.

Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics 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 Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics that contained HA antigen derived from a different clade of the same influenza subtype as the influenza pandemic strain may receive a single dose of Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics instead of two doses that are required in previously unvaccinated individuals (see section 5.1).

Paediatric population:

The safety and efficacy of Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics 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, 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 and to residues (eggs and chicken proteins, ovalbumin, kanamycin and neomycin 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 Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics 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 Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics with other H5N1 monovalent vaccines.

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 strains.

SRH antibody response against an homologous H5N1 Vietnam strain at day 43 reached all CHMP criteria for all 3 strains.

Co-administration was not associated with higher rates of local or systemic reactions compared to administration of Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics alone.

Therefore the data indicate that Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics may be co-administered with non-adjuvanted seasonal influenza vaccines (with injections made into opposite limbs).

There are no data on co-administration of Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics 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, 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

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

Limited data was obtained from women who became pregnant during the course of clinical trials with Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics or H1N1v vaccines adjuvanted with MF59C.1.

It is estimated that more than 90,000 women have been vaccinated during pregnancy with H1N1v vaccine Focetria which contains the same amount of adjuvant MF59C.1 as. Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics. 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 Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics 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.

There are no data regarding the use of Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics during breast-feeding. The potential benefits to the mother and risks to the infant should be considered before administering Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics during breast-feeding.

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 adults (18 years old and above).

The incidence of adverse reactions has been evaluated in six clinical trials involving approximately 4,000 adults and elderly receiving (Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics at least 7.5 µg HA, adjuvanted). There were 3678 subjects 18-60 years of age, 264 subjects 61-70 years of age, and 41 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 Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics 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.

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 ($\geq 1/10$)

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 ($< 1/10,000$)

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

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

These side effects usually disappear within 1-2 days without treatment.

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

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.

	Injection 1	Injection 2	Injection 3
	Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics	Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics	Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics
Toddlers (6-<36 months)	N=145	N=138	N=124
Any	76%	68%	80%
Local	47%	46%	60%
Systemic	59%	51%	54%
Fever $\geq 38^{\circ}\text{C}$ ($\geq 40^{\circ}\text{C}$)	0%	0%	0%
Any Other Adverse Event	54%	49%	35%
Children (3-<9 years)	N=96	N=93	N=85
Any	72%	68%	79%
Local	66%	58%	74%
Systemic	32%	33%	45%
Fever $\geq 38^{\circ}\text{C}$ ($\geq 40^{\circ}\text{C}$)	4%	2%	6%
Any Other Adverse Event	36%	31%	19%
Adolescents(9-<18 years)	N=93	N=91	N=83
Any	91%	82%	89%
Local	81%	70%	81%
Systemic	69%	52%	69%
Fever $\geq 38^{\circ}\text{C}$ ($\geq 40^{\circ}\text{C}$)	0%	1%	2%
Any Other Adverse Event	30%	27%	22%

Post-marketing surveillance

No post-marketing surveillance data are available following Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics administration.

The following additional adverse events were reported from post-marketing surveillance with Focetria H1N1v (licensed for use from 6 months of age and with a composition that is similar to Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics):

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 an MF59 seasonal adjuvanted trivalent vaccine with a composition similar to Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics (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

Transient thrombocytopenia.

Immune system disorders

Vasculitis with transient renal involvement and exudative erythema multiforme.

Nervous system disorders

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

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 Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics following a two-dose administration and booster.

Immune response against A/Vietnam/1194/2004 (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.

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

Anti-HA antibody (SRH)	Study V87P1 21 days after 2 nd dose N=149	Study V87P13 21 days after 2 nd dose N=197
Seroprotection rate (95%CI)*	85% (79-91)	91% (87-95)
Seroconversion rate (95%CI)*	85% (78-90)	78% (72-84)
Seroconversion factor (95%CI)**	7.74 (6.6-9.07)	4.03 (3.54-4.59)

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

* measured by SRH assay ≥ 25 mm²

** geometric mean ratios of SRH

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.

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 Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics 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 in subjects aged over 60 (limited number of subjects were above 70 years of age) measured by SRH assay assessed in two clinical studies were as follows:

Anti-HA antibody (SRH)	Study V87P1 21 days after 2 nd dose N=84	Study V87P13 21 days after 2 nd dose N=210
Seroprotection rate (95%CI)*	80% (70-88)	82% (76-87)
Seroconversion rate (95%CI)*	70% (59-80)	63% (56-69)
Seroconversion factor (95%CI)**	4.96 (3.87-6.37)	2.9 (2.53-3.31)

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

* measured by SRH assay ≥ 25 mm²

** geometric mean ratios of SRH

MN results against 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.

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 HI, SRH, and MN tests. Up to 50% of the elderly subjects immunised with Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics were seroprotected at six months.

A third (booster) dose of Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics 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 nd dose N=71	Study V87P2 Adults booster after 2 nd dose N=13	Study V87P1 Elderly booster after 2 nd dose N=38
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)

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

** geometric mean ratios of SRH

There is limited experience in the elderly

- Supportive data in adults

a) Cross reactivity

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

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

** geometric mean ratios of SRH

^o measured by HI assay ≥ 40

^{oo} 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/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.

b) Long term booster immune memory

A single vaccination with Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics (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 Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics 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 Prepandemic Influenza vaccine

(H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics dose, SRH CHMP criteria were achieved in all the vaccine schedule groups after 3 weeks from the 2nd vaccination. 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.

- 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 Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics 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)	97%	97%	89%	
	Day 43	(92-99)	(91-99)	(80-94)	
	GMR	129	117	67	
	Day 43 to Day 1	(109-151)	(97-142)	(51-88)	
SRH	% SC (95% CI)	97%	97%	89%	
	Day 43	(92-99)	(91-99)	(80-94)	
			N=133	N=91	N=90
	% SP (95% CI)	100%	100%	100%	
Day 43	(97-100)	(96-100)	(96-100)		
GMR (95% CI)	16	15	14		
Day 43 to Day 1	(14-18)	(13-17)	(12-16)		
% SC (95% CI)	98%	100%	99%		
Day 43	(95-100)	(96-100)	(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).

The European Medicines Agency has deferred the obligation to submit the results of studies with Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics (H5N1, A/Vietnam/1194/2004) 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. Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics containing HA from A/Vietnam/1194/2004 (homologous to the challenge strain) and an Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics -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 Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics were protected, and 94% of animals receiving a single dose of Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics 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 Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics 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,
Sodium citrate,
Citric acid,

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

3 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 compliance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Vaccines and Diagnostics S.r.l.

Via Fiorentina, 1

Siena, Italy.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/657/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 November 2010

10. DATE OF REVISION OF THE TEXT

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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 MANUFACTURING AUTHORISATION
HOLDER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Novartis Vaccines and Diagnostics S.r.l.
Via Fiorentina, 1 – 53100 Siena
Italy

Novartis Vaccines and Diagnostics S.r.l.
Loc. Bellaria – 53018 Rosia – Sovicille (SI)
Italy

Name and address of the manufacturer responsible for batch release

Novartis Vaccines and Diagnostics S.r.l.
Loc. Bellaria – 53018 Rosia – Sovicille (SI)
Italy

B. CONDITIONS OF THE MARKETING AUTHORISATION

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

• **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

• **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 3 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

PSURs

PSUR submission when Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics 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 (EC) No 726/2004 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, during a pandemic, resources needed for an in-depth evaluation of Periodic Safety Update Reports 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 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" (EMA/49993/2008), and any subsequent update.

Official batch release: in accordance with Article 114 Directive 2001/83/EC as amended, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARDBOARD BOX

1. NAME OF THE MEDICINAL PRODUCT

Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics 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: **Active Ingredients:** Influenza virus surface antigens (haemagglutinin and neuraminidase), propagated in eggs, of strain:

A/Vietnam/1194/2004 (H5N1)-like strain (NIBRG-14) 7.5 micrograms haemagglutinin

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

3. LIST OF EXCIPIENTS

Sodium chloride

Potassium chloride

Potassium dihydrogen phosphate

Disodium phosphate dihydrate

Magnesium chloride hexahydrate

Calcium chloride dihydrate

Sodium citrate

Citric acid

Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.

1 x single dose of 0.5 ml pre-filled syringe

10 x single dose of 0.5 ml pre-filled syringes

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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

Novartis Vaccines & Diagnostics S.r.l.
Via Fiorentina, 1
Siena, Italy.

12. MARKETING AUTHORISATION NUMBER

EU/1/10/657/001 1 prefilled syringe
EU/1/10/657/002 10 prefilled syringes

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

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

Prepandemic Influenza vaccine (H5N1)
H5N1 influenza vaccine
Intramuscular use

2. METHOD OF ADMINISTRATION

Gently shake before use.

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

Store in a refrigerator.
Novartis V&D S.r.l. – Italy

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics suspension for injection in pre-filled syringe Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted)

Read all of this leaflet carefully before you start receive this vaccine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

1. What Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics is and what it is used for
2. Before you receive Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics
3. How Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics is given
4. Possible side effects
5. How to store Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics
6. Further information

1. WHAT PREPANDEMIC INFLUENZA VACCINE (H5N1) (SURFACE ANTIGEN, INACTIVATED, ADJUVANTED) NOVARTIS VACCINES AND DIAGNOSTICS IS AND WHAT IT IS USED FOR

Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics 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 influenza (flu) pandemic 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, Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics may not fully protect all persons who are vaccinated.

2. BEFORE YOU RECEIVE PREPANDEMIC INFLUENZA VACCINE (H5N1) (SURFACE ANTIGEN, INACTIVATED, ADJUVANTED) NOVARTIS VACCINES AND DIAGNOSTICS

You should not receive Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics:

- if you have previously had a sudden life-threatening allergic reaction to any ingredient of Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics (these are listed at the end of the leaflet) 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) 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 have the vaccine provided that appropriate medical treatment is immediately available in case of an allergic reaction.

If you are not sure, talk to your doctor or nurse before having this vaccine.

Take special care with Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics:

- 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 Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics;
- if you are having a blood test to look for evidence of infection with certain viruses. In the first few weeks after vaccination with Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics the results of these tests may not be correct. Tell the doctor requesting these tests that you have recently been given Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics.
- in the presence of immune deficiencies Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics may be administered but a protective immune response may not be elicited.

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

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

Taking other medicines

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

Data obtained in adults showed that Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics can be given at the same time as non-adjuvanted seasonal influenza vaccines, with injections made into separate limbs. In such cases, you should be aware that the side effects may be more intense.

Pregnancy and breast-feeding

Limited data was obtained from women who became pregnant with Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics during the course of clinical trials.

Your doctor needs to assess the benefits and potential risks of giving you the vaccine if you are pregnant or breast-feeding. Tell your doctor if you are pregnant, think you may be pregnant, plan to become pregnant. You should discuss with your doctor whether you should receive Prepandemic

Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics.

Tell your doctor if you are breast-feeding and follow his advice.

Driving and using machines

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

Important information about some of the ingredients of Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics

This medicinal 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 PREPANDEMIC INFLUENZA VACCINE (H5N1) (SURFACE ANTIGEN, INACTIVATED, ADJUVANTED) NOVARTIS VACCINES AND DIAGNOSTICS 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 and elderly (18 years of age and above):

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

There is limited experience in children between 6 months and 17 years of age.

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.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics 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.

In the clinical trials with the vaccine, most side effects were mild in nature and short term. The side-effects are generally similar to those related to the seasonal flu vaccine.

The frequency of possible side effects listed below is defined using the following convention:

very common (affects more than 1 user in 10)

common (affects 1 to 10 users in 100)

uncommon (affects 1 to 10 users in 1,000)

rare (affects 1 to 10 users in 10,000)

very rare (affects less than 1 user in 10,000)

The side effects listed below have occurred with Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics in clinical studies in adults, including the elderly:

Very common:

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:

Bruising of the skin at the injection site, fever and nausea, generally feeling unwell and shivering.

Uncommon:

Flu like symptoms.

Rare:

Convulsions, eye swelling and 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)

A clinical study was conducted with the same vaccine in children. 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 Focetria H1N1v vaccine.

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 and diarrhoea.

Headache, dizziness, drowsiness, fainting.

Neurological disorders such as severe stabbing or throbbing pain along one or more nerves, tingling, fits, and 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 flu. These side effects may occur with Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics.

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), and 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.

If any of these side effects occur, please tell your doctor or nurse immediately.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE PREPANDEMIC INFLUENZA VACCINE (H5N1) (SURFACE ANTIGEN, INACTIVATED, ADJUVANTED) NOVARTIS VACCINES AND DIAGNOSTICS

Keep out of the reach and sight of children.

Do not use Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics contains

- Active Substance:
Influenza virus surface antigens (haemagglutinin and neuraminidase)* of strain:
A/Vietnam/1194/2004 (H5N1)-like strain (NIBRG-14) 7.5 micrograms** per 0.5 ml dose
* propagated in eggs
** expressed in microgram haemagglutinin.
- Adjuvant MF59C.1:
The vaccine contains per 0.5ml 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 Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics looks like and contents of the pack

Prepandemic Influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics 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

Novartis Vaccines and Diagnostics S.r.l.
Via Fiorentina, 1
Siena, Italy.

Manufacturer

Novartis Vaccines and Diagnostics S.r.l.
Loc. Bellaria - 53018 Rosia
Sovicille (SI), Italy.

This leaflet was last approved in {MM/YYYY}

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

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