ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Incellipan suspension for injection in pre-filled syringe
Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted, prepared in cell cultures).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

* propagated in Madin Darby Canine Kidney (MDCK) cells
** expressed in micrograms haemagglutinin.

Adjuvant MF59C.1 containing per 0.5 ml dose:

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

This vaccine complies with the WHO recommendations and EU decision in an officially declared pandemic situation.

Incellipan may contain trace residues of beta-propiolactone, polysorbate 80 and cetyltrimethylammonium bromide which are used during the manufacturing process (see section 4.3).

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection (injection).
Milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Incellipan is indicated for active immunisation against influenza in an officially declared pandemic.

Incellipan should be used in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Adults and children from 6 months of age

Incellipan is administered intramuscularly as a course of 2 doses of 0.5 ml each. It is recommended to administer the second dose 3 weeks after the first dose.

Elderly
No dose adjustment is required in elderly individuals ≥65 years of age.

Paediatric population (infants aged <6 months)
The safety and efficacy of Incellipan in infants aged less than 6 months have not yet been established. No data are available.

Booster dose
The need for a booster dose(s) following the primary vaccination schedule has not been established. Early waning of antibody levels has been observed, especially in adults (see section 5.1).

Method of administration

Incellipan should be administered intramuscularly.

For individuals 12 months of age and over, the preferred injection site is the deltoid muscle of the upper arm; for infants between 6 to less than 12 months of age, the preferred injection site is the anterolateral thigh.

The vaccine should not be injected intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions on handling and disposal, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1, or to possible trace residues such as beta-propiolactone, cetyltrimethylammonium bromide, and polysorbate 80.
History of an anaphylactic (i.e. life-threatening) reaction after a previous dose of an influenza vaccine.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered medicinal product should be clearly recorded.

Hypersensitivity and anaphylaxis

Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine. Close observation for at least 15 minutes is recommended following vaccination.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. However, the presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Limitations of vaccine effectiveness

There is no immune correlate of protection established for influenza A (H5N1).
Based on humoral immune responses to the vaccine strain A/turkey/Turkey/1/2005 after two doses of Incellipan, a protective immune response, as with any vaccine, may not be elicited in all vaccine recipients.
Some degree of cross-reactive immunity has been observed against H5N1 viruses of clades different to that of the vaccine strain. However, the degree of protection that may be elicited to H5N1 strains of other subtypes or clades is unknown (see section 5.1).

Duration of protection

The duration of protection following the primary vaccination schedule is unknown.

A reduction of antibody titres was observed when assessed 6 and 12 months after the primary vaccination series with the A/turkey/Turkey/1/2005 (H5N1) strain.

Immunocompromised individuals

The efficacy, safety and immunogenicity of the vaccine have not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The immune response of Incellipan may be lower in immunosuppressed individuals and may be insufficient to provide protection.

Convulsions

While no postmarketing data are available from the use of Incellipan, cases of convulsion (with and without fever) were reported during the 2009 pandemic for H1N1 vaccines manufactured with the MF59 adjuvant, similarly used in Incellipan.

The majority of febrile convulsions occurred in paediatric subjects. Some cases were observed in subjects with a history of epilepsy. Particular attention should be given to subjects suffering from epilepsy and the physician should inform the vaccine recipients (or parents) about the possibility to experience convulsion. (see section 4.8).

Excipients with known effect

Sodium
This vaccine contains less than 1 mmol of sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

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

'potassium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. If Incellipan is given at the same time as another injectable vaccine(s), the vaccine(s) should always be administered to separate limbs. It should be noted that adverse reactions may be intensified.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of Incellipan in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, see section 5.3.

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

Breast-feeding

Incellipan has not been evaluated during breast-feeding. The vaccine is not expected to be excreted in human milk and no effects on the breastfed newborn/infant are anticipated.

Fertility

A reproductive and developmental toxicity study in female rabbits dosed with Incellipan revealed no impairment of fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Adults 18 years of age and older
The most common local and systemic reactions reported in adults within 7 days following administration were injection site pain (51%), fatigue (22%), headache (20%), malaise (19%), myalgia (14%) and arthralgia (11%).

Severe reactions in subjects receiving aH5N1c were reported in 1% or fewer subjects for each reaction. Reactogenicity was higher after the first dose than after the second dose.

Tabulated list of adverse reactions

The frequencies of adverse reactions are based on three clinical studies in 3 579 subjects (see section 5.1).

The adverse reactions are listed according to the following MedDRA frequency convention and system organ class: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1 000 to <1/100).

Table 1: Adverse reactions reported in adults 18 years of age and older

MedDRA system organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1 000 to <1/100)
Blood and lymphatic system disorders			Lymphadenopathy
Nervous system disorders	Headache		Dizziness
Gastrointestinal disorders		Loss of appetite, nausea	Diarrhoea, vomiting
Skin and subcutaneous tissue disorders			Rash, pruritus
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia		
General disorders and administration site conditions	Injection site pain, fatigue, malaise	Chills, injection site bruising, injection site induration, fever	Injection site erythema, injection site haemorrhage

Elderly population

Elderly individuals 65 years and older generally reported fewer solicited local and systemic reactions compared to younger adults.

Paediatric population 6 months to less than 18 years of age

Clinical safety data for Incellipan in children 6 months to less than 18 years of age was collected in Study V89_11.

This was a phase 2, randomised, controlled, observer-blind multicentre study conducted in children 6 months to less than 18 years of age who received either two 0.5 mL (7.5 mcg HA of H5N1 with 0.25 mL MF59) or 0.25 mL (3.75 mcg HA of H5N1 with 0.125 mL MF59) doses of vaccine, 21 days apart.

In total, 658 subjects in the safety population received at least one dose (7.5 mcg dose, N=329; 3.75 mcg dose, N=329).

Solicited local and systemic adverse reactions were collected for 7 days after vaccination following each vaccination in all children, divided into two age cohorts (6 months to <6 years, and 6 to <18 years of age).

In both the 7.5 mcg and 3.75 mcg dose groups, the majority of solicited local and systemic adverse reactions were mild or moderate in intensity and resolved within a few days. The frequency of solicited local and systemic adverse reactions was similar between the 7.5 mcg and 3.75 mcg doses.

The most common (≥10 %) solicited local and systemic reactions reported within 7 days following administration of Incellipan in children 6 months to less than 6 years of age were tenderness at the injection site (56%), irritability (30%), sleepiness (25%), change in eating habits (18%) and fever (16%).

The most common (≥10 %) solicited local and systemic reactions reported within 7 days following administration of Incellipan in children 6 to less than 18 years of age were injection site pain (68%), myalgia (30%), fatigue (27%), malaise (25%), headache (22%), loss of appetite (14%), nausea (13%), and arthralgia (13%).

Local and systemic adverse reactions reported in subjects who received either 7.5 mcg or 3.75 mcg doses of aH5N1c from Study V89_11 are shown below in Table 2.

The adverse reactions reported are listed according to the following MedDRA frequency convention and system organ class: Very common (≥1/10); Common (≥1/100 to <1/10).

Table 2: Adverse reactions in children 6 months to less than 18 years of age

MedDRA system organ class	Adverse reactions	Frequency	
		6 months to <6 years	6 to <18 years
Nervous system disorders	Headache		Very common
Gastrointestinal disorders	Nausea		Very common
	Decreased appetite[1]	Very common	Very common
	Vomiting	Common	Common
	Diarrhoea	Common	Common
Musculoskeletal and connective tissue disorders	Myalgia		Very common
	Arthralgia		Very common
General disorders and administration site conditions	Injection site pain/tenderness[2]	Very common	Very common
	Injection site erythema	Common	Common
	Injections site induration	Common	Common
	Fatigue		Very common
	Somnolence[3]	Very common	
	Malaise		Very common
	Irritability	Very common	
	Fever	Very common[4]	Common

[1] The terms, ¨Change in eating habits¨ and ¨Loss of appetite¨, were collected in children 6 months to <6 years of age and 6 to <18 years of age, respectively.
[2] Injection site tenderness was collected in children 6 months to <6 years of age.
[3] The term, ¨Sleepiness¨, was collected in children 6 months to <6 years of age.
[4] In the age group 6 months to <6 years of age, fever was reported at a rate of 16% in subjects who received the 7.5 mcg dose and 8% in subjects who received the 3.75 mcg dose.

Description of selected adverse reactions
There is no post-marketing experience following administration of Incellipan. However, the following post-marketing adverse events have been reported after use of influenza vaccines in general (Table 3).

Table 3: Post-marketing experience reported after use of influenza vaccines in general

MedDRA system organ class	Adverse reaction[1]
Immune system disorders	Allergic reactions, such as immediate hypersensitivity, anaphylaxis including dyspnoea, bronchospasm, laryngeal oedema, in rare cases leading to anaphylactic shock
Nervous system disorders	Neuralgia, paraesthesia, neuritis, convulsions, encephalomyelitis, Guillain-Barré syndrome, vaccination anxiety-related reactions including presyncope and syncope
Vascular disorders	Vasculitis which may be associated with transient renal involvement
Skin and subcutaneous tissue disorders	Generalised skin reactions such as urticaria, non-specific rash, and local allergic reactions including angioedema
General disorders and administration site conditions	Extensive swelling of vaccinated limb

[1]Frequency not known (cannot be estimated from the available data)

In addition, the following adverse events were reported from post-marketing surveillance with aH1N1 (a monovalent influenza vaccine licensed for use from 6 months of age during the 2009 influenza pandemic and containing the same MF59 adjuvant as Incellipan) (Table 4).

Table 4: Post-marketing experience reported after use a similar pandemic influenza vaccine (aH1N1)

MedDRA system organ class	Adverse reaction[1]
Nervous system disorders	Somnolence
Cardiac disorders	Palpitation, tachycardia
Respiratory, thoracic and mediastinal disorders	Cough
Gastrointestinal disorders	Abdominal pain
Musculoskeletal and connective tissue disorders	Muscular weakness, pain in extremities
General disorders and administration site conditions	Asthenia

[1]Frequency not known (cannot be estimated from the available data)

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

There is no experience of overdose with Incellipan vaccine. In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines, influenza vaccine, ATC Code: J07BB02.

This section describes the clinical experience with the pandemic preparedness vaccine.

Pandemic preparedness vaccines contain influenza antigens that are different from those in the currently circulating influenza viruses. These antigens can be considered as "novel" antigens and simulate a situation where the target population for vaccination is immunologically naïve. Data obtained with the pandemic preparedness vaccine will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical immunogenicity, safety and reactogenicity data obtained with pandemic preparedness vaccines are relevant for the pandemic vaccines.

Adults

Study V89_18 was a phase 3, randomised, observer-blind, multicentre, controlled study conducted in the United States in adults 18 years of age and older, who received either aH5N1c or sodium chloride 9 mg/mL (0.9%) solution for injection placebo, 21 days apart. In total, 2 988 subjects (18 to <65 years N=1 488; ≥65 years N=1 500) in the per protocol population received both doses of aH5N1c (N=2 249) or placebo (N=739). Haemagglutination inhibition (HI) antibody titres against the A/turkey/Turkey/1/2005 (H5N1) strain were evaluated in sera obtained 21 days after the second dose.

HI titres were assessed according to prespecified criteria for the proportion of subjects with seroconversion (defined as a pre-vaccination HI titre <1:10 and post-vaccination HI titre ≥1:40 or a pre-vaccination HI titre ≥1:10 and ≥4-fold increase in HI titre) and the proportion of subjects with an HI titre ≥1:40. Assessment of the proportion of subjects with seroconversion or an HI titre ≥1:40 after vaccination was performed by age group (18 to <65 years and ≥65 years). Success criteria required the lower bound of the 2-sided 95% CI for the proportion of subjects with seroconversion, to be ≥40% for subjects 18 to less than 65 years, and ≥30% for subjects ≥65 years of age. For the proportion of subjects with an HI titre >1:40, the lower bound of the 2-sided 95% CI was required to be ≥70% for subjects ≥18 to less than 65 years of age, and ≥60% for subjects ≥65 years of age.

In subjects 18 to less than 65 years of age and subjects ≥65 years of age, the prespecified criteria for proportion of subjects with seroconversion and an HI titre ≥1:40 were met 21 days after the second vaccination (Table 5). In Study V89_04 for adults 18 to less than 65 years of age, and Study V89_13 for adults 65 years of age and older, comparable immunogenicity results were observed.

Table 5. Seroconversion rates, percentage of subjects with HI titres ≥1:40 and geometric mean titre ratios (GMR) following aH5N1c or placebo (21 days after 2 vaccinations) (PPS[a] – study V89_18)

	Adults 18 to less than 65 years of age		**Adults 65 years of age and older**	
	aH5N1c (N=1 076)	**Placebo (N=349)**	**aH5N1c (N=1 080)**	**Placebo (N=351)**
Seroconversion[b] (95% CI)	79.9% (**77.4**; 82.3)	0.3% (0.0; 1.6)	54.0% (**51.0**; 57.0)	1.7% (0.6; 3.7)
HI titre ≥1:40 (95% CI)	95.0% (**93.4**, 96.2)	8.5% (5.9, 12.1)	85.7% (**83.3**, 87.9)	20.8% (16.6, 25.8)
GMR Day 43/Day 1[c] (95% CI)	12.7 (11.9, 13.5)	0.8 (0.7, 0.9)	4.9 (4.6, 5.2)	0.8 (0.8, 0.9)

[a] PPS: Per Protocol Set, subjects who correctly received 2 doses of aH5N1c according to the study protocol
[b] Seroconversion is defined as a pre-vaccination HI titre <1:10 and post-vaccination HI titre ≥1:40 or a pre-vaccination HI titre ≥1:10 and ≥4-fold increase in HI titre.
[c] Geometric mean HI titres on Day 43 compared to Day 1

Bold shows that the prespecified criterion was met, ie, a lower bound of the 2-sided 95% confidence interval for seroconversion ≥40%, and for the proportion of subjects with HI antibody titres of ≥1:40 a lower bound of the 2-sided 95% confidence interval ≥70% for subjects 18 to less than 65 years and ≥60% for subjects 65 years and older.

The MicroNeutralisation (MN) assay was used to measure immunological response against the homologous strain in a subset of 76 adults 18 to <65 years of age in Study V89_18. Using the MN assay an at least 4-fold increase from baseline titres at Day 43 was achieved in 90% of subjects and a 24-fold increase in GMTs was achieved on Day 43 compared to Day 1.

A reduction of antibody titres was observed 6 months after the primary vaccination series with the A/turkey/Turkey/1/2005 (H5N1) strain, with GMRs of 1.53 [95% CI: 1.44, 1.61] in adults 18 to <65 years of age and 0.97 [95% CI: 0.91, 1.02] in adults ≥65 years of age. Slightly higher but overall comparable GMRs were observed at the 12-month time point of the phase 2 trials V89_04 (GMR 1.95 [95% CI: 1.73, 2.19] in adults 18 to <65 years of age) and V89_13 (GMR 1.97 [97.5% CI: 1.76, 2.2] in adults ≥65 years of age). No data are available beyond 12 months.

Cross reactivity data in adults

Cross-reactive immune response elicited by A/turkey/Turkey/1/2005 (clade 2.2.1)
In the phase 2 studies, V89_04 and V89_13, immune responses were evaluated against five H5N1 heterologous strains: A/Anhui/1/2005 (clade 2.3.4); A/Egypt/N03072/2010 (clade 2.2.1); A/Hubei/1/2010 (clade 2.3.2); A/Indonesia/5/2005 (clade 2.1.3) and A/Vietnam/1203/2004 (clade 1) three weeks after the second vaccination. HI geometric mean titres (GMTs) on Day 43 compared to Day 1 increased between 2- and 7.3-fold in subjects 18 to <65 years of age (Study V89_04), and between 1.5- and 4.8-fold in subjects ≥65 years of age (Study V89_13). The percentage of subjects with seroconversion or an HI titre ≥1:40 at Day 43 ranged from 28% to 64% in subjects 18 to <65 years of age and from 17% to 57% in subjects ≥65 years of age. Table 6 presents data on immune responses against the H5N1 heterologous strains.

Table 6. Seroconversion rates, percentage of subjects with HI titres ≥1:40 and geometric mean titre ratios (GMR) following aH5N1c (21 days after 2 vaccinations) against heterologous H5N1 strains in subjects 18 to <65 years of age and ≥65 years of age (FAS[a] – Study V89_04 and V89_13)

	Adults 18 to less than 65 years of age (V89_04) N=69				
	A/Anhui/ 1/2005	**A/Egypt/ N03072/2010**	**A/Hubei/ 1/2010**	**A/Indonesia/ 5/2005**	**A/Vietnam/ 1203/2004**
Seroconversion[b] (97.5% CI)	28% (16, 41)	55% (41, 69)	55% (41, 69)	35% (22; 49)	52% (38, 66)
HI titre ≥1:40 (97.5% CI)	28% (16, 41)	58% (44, 71)	64% (50, 76)	35% (22, 49)	54% (40, 67)
GMR Day 43/Day 1[c] (95% CI)	2.1 (1.3, 3.4)	6.5 (3.6, 12)	7.3 (4.0; 13)	3.1 (1.8, 5.4)	7.0 (3.8, 13)
	Adults ≥65 years of age (V89_13) N=35				
Seroconversion[b] (95% CI)	17% (6, 36)	43% (24, 63)	46% (27, 66)	26% (11, 46)	43% (24, 63)
HI titre ≥1:40 (95% CI)	17% (6, 36)	49% (29, 68)	57% (37, 76)	26% (11, 46)	51% (32, 71)
GMR Day 43/Day 1[c] (95% CI)	1.5 (0.9; 2.6)	3.6 (1.6; 8.2)	4.8 (2.3; 10)	2.1 (1.1; 3.8)	4.3 (2.0; 9.2)

[a] FAS: Full Analysis Set, subjects who received at least one study vaccination and provided immunogenicity data at day 1 and day 43
[b] Seroconversion is defined as a pre-vaccination HI titre <1:10 and post-vaccination HI titre ≥1:40 or a pre-vaccination HI titre ≥1:10 and ≥4-fold increase in HI titre.
[c] Geometric mean HI titres on Day 43 compared to Day 1

Using the MicroNeutralisation (MN) assay against the 5 heterologous strains, an at least 4-fold increase from baseline titres at Day 43 was achieved by 32% to 88% of subjects 18 to <65 years of age, and by 26% to 74% of subjects ≥65 years of age. MN GMTs on Day 43 compared to Day 1 increased between 4.8- and 34-fold in subjects 18 to <65 years of age (Study V89_04), and between 3.7- and 12-fold in subjects ≥65 years of age (Study V89_13).

Paediatric population 6 months to less than 18 years of age

Immunogenicity data for aH5N1c in children 6 months to <18 years of age was assessed in Study V89_11. This was a randomised, controlled, observer-blind multicentre study conducted in children 6 months to less than 18 years of age who received two doses of either 7.5 mcg HA of H5N1 with MF59 per 0.5 mL or 3.75 mcg HA of H5N1 with MF59 per 0.25 mL, 21 days apart.

In total, 577 subjects in the full analysis population received the 7.5 mcg dose (N=329) or 3.75 mcg dose (N=329). The subjects were divided into three age cohorts, 6 to <36 months (N=177), 3 to <9 years (N=193), and 9 to <18 years (N=207); 53% of the subjects were male. 73% of the participants were Asian, 22% were White, 3% were Black or African American. HI antibody titres against the A/turkey/Turkey/1/2005 (H5N1) strain were evaluated in sera obtained 21 days after the second dose in three age cohorts (6 to <36 months, 3 to <9 years, and 9 to <18 years).

The proportion of subjects with seroconversion and an HI titre of ≥1:40 after vaccination was evaluated according to prespecified criteria. The success criteria for proportion of subjects with seroconversion were that the lower bound of the 2-sided 97.5% CI should be ≥40% and for the proportion of subjects with an HI titre >1:40, the lower bound of the 2-sided 97.5% CI should be ≥70% for all three age cohorts.

In all three age cohorts (6 to <36 months, 3 to <9 years, and 9 to <18 years) the prespecified criteria for proportion of subjects with seroconversion and an HI titre ≥1:40 were met 21 days after the second vaccination with either the 7.5 mcg or 3.75 mcg dose. Table 7 presents data for the recommended dose.

Table 7. Seroconversion rates, percentage of subjects with HI titres ≥1:40 and geometric mean titre ratios (GMR) following vaccination with aH5N1c in Study V89_11 (FAS[a])

Formulation: 7.5 mcg HA / 100% MF59				
	Overall population	**Age subgroups**		
	6 months to <18 years	**6 to <36 months**	**3 to <9 years**	**9 to <18 years**
Seroconversion[b] (97.5% CI)[c]	96% (**93**-98) N=279	99% (**94**; 100) N=84	98% (**92**; 100) N=93	92% (**85**; 97) N=102
HI titre ≥1:40 (97.5% CI)[c]	96% (**92**-98) N=287	98% (**92**; 100) N=91	98% (**93**; 100) N=94	92% (**85**; 97) N=102
GMR Day 43/Day 1[d] (97.5% CI)[c]	262 (190-361)	302 (192-476)	249 (153-404)	186 (105-328)

	N=279	N=84	N=93	N=102
Formulation: 3.75 mcg HA / 50% MF59				
Seroconversion[b] (97.5% CI)[c]	86% (81-90) N=288	94% (87-98) N=85	86% (77-92) N=98	79% (70-86) N=105
HI titre ≥1:40 (97.5% CI)[c]	86% (81-90) N=288	94% (87-98) N=85	86% (77-92) N=98	79% (70-86) N=105
GMR Day 43/Day 1[d] (97.5% CI)[c]	84 (61-116) N=288	116 (74-181) N=85	73 (44-121) N=98	58 (34-101) N=105

[a] FAS: Full Analysis Set, subjects who received at least one 7.5 or 3.75 mcg dose of aH5N1c and provided immunogenicity data at day 1 and day 43.
[b] Seroconversion is defined as a pre-vaccination HI titre <1:10 and post-vaccination HI titre ≥1:40 or a pre-vaccination HI titre ≥1:10 and ≥4-fold increase in HI titre.
[c] 95% CI used for age subgroups
[d] Geometric mean HI titres on Day 43 compared to Day 1
Bold shows that the prespecified criterion was met, ie, a lower bound of the 2-sided 97.5% confidence interval for seroconversion ≥40% and for the proportion of subjects with an HI titre of ≥1:40 a lower bound of the 2-sided 97.5% confidence interval ≥70%.

The MicroNeutralisation (MN) assay was used to evaluate immunological response against the homologous strain (A/turkey/Turkey/1/2005) in subjects 6 months to <18 years of age (N=69) who received the 7.5 mcg dose in study V89_11. Using the MN assay an at least 4-fold increase from baseline titres at Day 43 was achieved in 100% of subjects and a 257-fold increase in GMTs was achieved on Day 43 compared to Day 1.

A reduction of antibody titres was observed when assessed 12 months after the primary vaccination series with the A/turkey/Turkey/1/2005 (H5N1) strain (GMRs 7.5 mcg dose: 12 [97.5% CI: 8.76, 17]; 3.75 mcg dose: 5.62 [97.5% CI: 4.05, 7.81]), but the GMRs were still higher compared to the adult population. No data are available beyond 12 months.

Cross reactivity data in the paediatric population 6 months to less than 18 years of age

Cross-reactive immune response elicited by A/turkey/Turkey/1/2005 (clade 2.2.1)
In subjects 6 months to less than 18 years of age (Study V89_11), immune responses were evaluated against five H5N1 heterologous strains: A/Anhui/1/2005 (clade 2.3.4); A/Egypt/N03072/2010 (clade 2.2.1); A/Hubei/1/2010 (clade 2.3.2); A/Indonesia/5/2005 (clade 2.1.3) and A/Vietnam/1203/2004 (clade 1) three weeks after the second vaccination. HI GMTs on Day 43 increased between 8- and 40-fold compared to Day 1. The percentage of subjects with seroconversion or an HI titre ≥1:40 at Day 43 ranged from 32% to 72% in subjects 6 months to <18 years of age. Table 8 presents data on immune responses against the H5N1 heterologous strains.

Table 8. Seroconversion rates, percentage of subjects with HI titres ≥1:40 and geometric mean titre ratios (GMR) following aH5N1c (21 days after 2 vaccinations) against heterologous H5N1 strains in subjects 6 months to <18 years of age (FAS[a] – Study V89_11)

	Children 6 months to < 18 years of age (V89_11) N=69				
	A/Anhui/	**A/Egypt/**	**A/Hubei/**	**A/Indonesia/**	**A/Vietnam/**

	1/2005	N03072/2010	1/2010	5/2005	1203/2004
Seroconversion[b] (97.5% CI)	32% (20, 46)	72% (59, 84)	54% (40, 67)	36% (24; 50)	54% (40, 68)
HI titre ≥1:40 (97.5% CI)	32% (20, 46)	72% (59, 84)	54% (40, 67)	36% (24, 50)	54% (40, 68)
GMR Day 43/Day 1[c] (97.5% CI)	8.4 (4.0; 17)	40 (15; 109)	34 (11; 105)	11 (4.9; 25)	23 (8.5; 60)

[a] FAS: Full Analysis Set, subjects who received at least one study vaccination and provided immunogenicity data at day 1 and day 43
[b] Seroconversion is defined as a pre-vaccination HI titre <1:10 and post-vaccination HI titre ≥1:40 or a pre-vaccination HI titre ≥1:10 and ≥4-fold increase in HI titre.
[c] Geometric mean HI titres on Day 43 compared to Day 1

MN assay results against the 5 heterologous strains showed a substantial percentage of paediatric subjects achieving an at least 4-fold increase in MN titres at Day 43, ranging from 83% to 100%. MN GMTs on Day 43 compared to Day 1 increased between 13- and 160-fold in subjects 6 months to <18 years of age (Study V89_11).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Incellipan in one or more subsets of the paediatric population in prevention of pandemic influenza (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on repeat-dose and reproductive and developmental toxicity studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

For the adjuvant, see section 2

6.2 Incompatibilities

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

6.3 Shelf life

1 year

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze. Discard the vaccine if it has been frozen.
Keep the pre-filled syringe in the outer carton 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 (bromobutyl rubber) and fitted with a Luer Lock system. Needles are not included.
Pack of 10 pre-filled syringes. Each pre-filled syringe contains 1 dose of 0.5 ml.

6.6 Special precautions for disposal and other handling

Gently shake before use. After shaking, the normal appearance of the vaccine is a milky white suspension.

Visually inspect the content of each pre-filled syringe for particulate matter and/or variation in appearance prior to administration. If either condition is observed, do not administer the vaccine.

To use the pre-filled syringe supplied with a Luer Lock system, remove the tip cap by unscrewing it in a counter-clockwise direction. Once the tip cap is removed, attach a needle to the syringe by screwing it on in a clockwise direction until it locks. Use a sterile needle of the appropriate size for intramuscular injection. Once the needle is locked in place, remove the needle protector and administer the vaccine.

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

7. MARKETING AUTHORISATION HOLDER

Seqirus Netherlands B.V.
Paasheuvelweg 28
1105BJ Amsterdam
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1807/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATIONS TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Seqirus Inc.
475 Green Oaks Parkway
Holly Springs
NC 27540
United States

Name and address of the manufacturer responsible for batch release

Seqirus Netherlands B.V.
Paasheuvelweg 28
1105BJ Amsterdam
Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy of Incellipan, the MAH should conduct a non-interventional observational effectiveness study in children and adults against laboratory confirmed influenza during the next declared pandemic. The MAH should submit the final results of this study.	After declaration of a pandemic in the EU and after implementation of the pandemic vaccine

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARDBOARD BOX FOR SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Incellipan suspension for injection in pre-filled syringe
Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted, prepared in cell cultures)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose (0.5 ml) contains: Influenza virus surface antigens (haemagglutinin and neuraminidase), inactivated, propagated in Madin Darby Canine Kidney (MDCK) cells, and adjuvanted with MF59C.1, of strain:

A/turkey/Turkey/1/2005 (H5N1) 7.5 micrograms haemagglutinin

Adjuvant MF59C.1: squalene, polysorbate 80, sorbitan trioleate, sodium citrate, citric acid.

3. LIST OF EXCIPIENTS

Excipients: sodium chloride, potassium chloride, magnesium chloride hexahydrate, disodium phosphate dihydrate, potassium dihydrogen phosphate, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.

10 pre-filled syringes (0.5 ml) without needle

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Gently shake before use.

Intramuscular 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. Keep the pre-filled syringe in the outer carton 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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Seqirus Netherlands B.V.
Paasheuvelweg 28
1105BJ Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1807/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL FOR SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Incellipan injection
Pandemic influenza vaccine (H5N1)

IM

2. METHOD OF ADMINISTRATION

Intramuscular use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Incellipan suspension for injection in pre-filled syringe
Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted, prepared in cell cultures)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Incellipan is and what it is used for

Incellipan is a vaccine intended to be given to prevent influenza (flu) in an officially declared pandemic.

Pandemic flu is a type of influenza that happens at intervals that vary from less than 10 years to many decades. It spreads rapidly around the world. The signs of pandemic flu are similar to those of ordinary flu but may be more serious.

It is used to prevent flu caused by the H5N1 type of the virus.

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

2. What you need to know before you receive Incellipan

You should not receive Incellipan:
- if you are allergic to
  - the active ingredients or any of the other ingredients of this medicine (listed in section 6),
  - beta-propiolactone, polysorbate 80 or cetyltrimethylammonium bromide (CTAB), which are trace residues from the manufacuring process.
- if you have had a severe allergic reaction (e.g., anaphylaxis) to previous influenza vaccination.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before receiving this vaccine.

BEFORE receiving this vaccine

- Your doctor or nurse will make sure that appropriate medical treatment and supervision is readily available in case of a rare anaphylactic reaction (a very severe allergic reaction with symptoms such as difficulty in breathing, dizziness, a weak and rapid pulse and skin rash) after Incellipan is given.
- You should tell your doctor or nurse if you are feeling nervous about the vaccination process or have ever fainted following an injection.
- You should tell your doctor or nurse if you have an acute illness which includes fever as a symptom. Your doctor may decide to delay your vaccination until your fever is gone. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.
- You should tell your doctor or nurse if you have a bleeding problem, bruise easily or you use a medicine to prevent blood-clots.
- You should tell your doctor or nurse if your immune system is impaired, or if you are having treatment that affects the immune system, e.g., with medicine against cancer (chemotherapy) or corticosteriod medicines (see section "Other medicines and Incellipan).
- Your doctor should inform you about the posibility to experience convulsion, in particular if you have had previous history of epilepsy.

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

Children aged less than 6 months of age
The vaccine is currently not recommended in children aged less than 6 months as safety and efficacy in this age group have not been established.

Other medicines and Incellipan
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.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or nurse for advice before taking this vaccine. Your doctor needs to assess the benefits and potential risks of giving you the vaccine.

There is no experience of using Incellipan in breast-feeding women. Incellipan is not expected to pass into breast-milk and therefore no effects on breast-fed infants are anticipated.

Driving and using machines
Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect the ability to drive and use machines. Wait until these effects have worn off before driving and using machines.

Incellipan contains sodium and potassium
This vaccine contains less than 1 mmol of sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

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

3. How Incellipan is given

Your doctor or nurse administers the vaccine in accordance with official recommendations.

Adults and children 6 months of age and older:
One dose (0.5 ml) of the vaccine will be injected into the upper arm (deltoid muscle) or upper thigh, depending on your age and muscle mass.

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

4. Possible side effects

Like all medicines, Incellipan can cause side effects, although not everybody gets them.

Very serious side effects
Allergic reactions may occur following vaccination, and these may be severe. Tell your doctor immediately or go to the emergency department at your nearest hospital if you experience the following signs or symptoms of an allergic reaction:
- difficulty in breathing,
- dizziness,
- a weak and rapid pulse
- skin rash

If you experience these symptoms, you may need urgent medical attention or hospitalisation.

Other side effects
Other side effects which may occur with Incellipan include those listed below.

Adults 18 years of age and older
The following side effects have occurred with Incellipan in clinical studies in adults, including the elderly:

Very common (may affect more than 1 in 10 people)
- Injection site pain
- Muscle pain (myalgia)
- Joint pain (arthralgia)
- Headache
- Fatigue
- Generally feeling unwell (malaise)

Common (may affect up to 1 in 10 people):
- Feeling sick (nausea)
- Loss of appetite
- Chills
- Injection site bruising
- Hardening of the skin at the injection site (induration)
- Fever

Uncommon (may affect up to 1 in 100 people):
- Swollen lymph nodes (lymphadenopathy)
- Dizziness
- Diarrhoea
- Vomiting
- Rash
- Itching (pruritis)
- Injection site redness (erythema)
- Injection site bleeding (haemorrhage)

Elderly subjects, 65 years of age and older, generally reported fewer reactions compared to younger adults.

Children 6 months to less than 18 years of age
The side effects below were reported in a clinical study with children 6 months to less than 18 years of age.

6 months to less than 6 years of age

Very common
- Decreased appetite
- Injection site tenderness
- Sleepiness
- Irritability
- Fever

Common
- Injection site redness (erythema)
- Hardening of the skin at the injection site (induration)
- Vomiting
- Diarrhoea

6 to less than 18 years of age

Very common
- Headache
- Nausea
- Decreased appetite
- Muscle pain (myalgia)
- Joint pain (arthralgia)
- Injection site pain
- Fatigue
- Generally feeling unwell (malaise)

Common
- Injection site redness (erythema)
- Hardening of the skin at the injection site (induration)
- Fever
- Vomiting
- Diarrhoea

The following additional side effects have been reported with use with seasonal influenza vaccines in general and with a pandemic vaccine similar to Incellipan.

- Temporary low blood platelet count which can result in bleeding or bruising (transient thrombocytopenia)
- 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.
- Neurological disorders such as, severe stabbing or throbbing pain along one or more nerves (neuralgia), tingling (paraesthesia), inflammation of the nerves (neuritis), fits (convulsions), inflammation of the central nervous system (encephalomyelitis), a type of paralysis (Guillain-Barré syndrome), fainting (syncope) or feeling about to faint (presyncope), sleepiness (somnolence)
- Irregular or forceful heartbeat (palpitations), faster than normal heartbeat (tachycardia)

- Inflammation of the blood vessels which can cause skin rashes, joint pain and kidney problems (Vasculitis)
- Generalised skin reactions including hives (urticaria), non-specific rash, abnormal swelling of the skin, usually around the eyes, lips, tongue, hands or feet, due to an allergic reaction (angioedema)
- Extensive swelling of the vaccinated limb
- Cough
- Pain in extremities, weakness of the muscles
- Pain in abdomen
- General weakness (asthenia)

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 Incellipan

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

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

Store in a refrigerator (2°C - 8°C). Do not freeze. Discard if the vaccine has been frozen. Keep the pre-filled syringe in the original carton in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Incellipan contains

- Active substance:
The active ingredients of the vaccine are purified viral proteins (called haemagglutinin and neuraminidase) prepared from the strain of influenza virus that complies with the World Health Organisation recommendations and EU decision in an officially declared Pandemic situation.

One dose (0.5 ml) of the vaccine contains 7.5 micrograms of haemagglutinin from the influenza virus strain, A/turkey/Turkey/1/2005 (H5N1) which has been propagated in Madin Darby Canine Kidney (MDCK) cells (this is the special cell culture in which the influenza virus is grown).

Adjuvant: MF59C.1 is included in this vaccine as an adjuvant. Adjuvants are substances included in certain vaccines to accelerate, improve and/or prolong the protective effects of the vaccine. MF59C.1 is an adjuvant that contains squalene, polysorbate 80, sorbitan trioleate, sodium citrate and citric acid.

- Other ingredients:
The other ingredients are: sodium chloride, potassium chloride, magnesium chloride hexahydrate, disodium phosphate dihydrate, potassium dihydrogen phosphate, and water for injections, see section 2 Incellipan contains sodium and potassium.

What Incellipan looks like and contents of the pack

Incellipan is a milky-white suspension.

It is provided in a ready-to-use syringe, containing a single dose (0.5 ml) for injection, in a pack of 10 pre-filled syringes and fitted with a Luer Lock system. Needles are not included.

Marketing Authorisation Holder and Manufacturer
Seqirus Netherlands B.V.
Paasheuvelweg 28
1105BJ Amsterdam
Netherlands

This leaflet was last revised in

Incellipan has been given "conditional approval".
This means that there is more evidence to come for this medicine.
The European Medicines Agency will review any new information on this medicine at least every year and this leaflet will be updated as necessary.

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

The following information is intended for healthcare professionals only:

Appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

Gently shake before use. After shaking, the normal appearance of Incellipan is a milky-white suspension.

The vaccine should be visually inspected for particulate matter and discoloration prior to administration. In the event of any foreign particulate matter and/or variation of physical aspect being observed, do not administer the vaccine.

To use the pre-filled syringe without a needle supplied with a Luer Lock system, remove the tip cap by unscrewing it in a counter-clockwise direction. Once the tip cap is removed, attach a needle to the syringe by screwing it on in a clockwise direction until it locks. Use a sterile needle of the appropriate size for intramuscular injection. Once the needle is locked in place, remove the needle protector and administer the vaccine.