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

Flucelvax Tetra - suspension for injection in pre-filled syringe
Influenza vaccine (surface antigen, inactivated, prepared in cell cultures)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Influenza virus surface antigens (haemagglutinin and neuraminidase), inactivated, of the following strains*:

A/Brisbane/02/2018 (H1N1)pdm09 - like strain (A/Idaho/07/2018) 15 micrograms HA**

A/Kansas/14/2017 (H3N2) - like strain (A/Indiana/08/2018) 15 micrograms HA**

B/Colorado/06/2017 - like strain (B/Iowa/06/2017) 15 micrograms HA**

B/Phuket/3073/2013 - like strain (B/Singapore/INFTT-16-0610/2016) 15 micrograms HA**

per 0.5 ml dose
…….
* propagated in Madin Darby Canine Kidney (MDCK) cells
** haemagglutinin

The vaccine complies with the World Health Organisation (WHO) recommendation (northern hemisphere) and EU recommendation for the 2019/2020 season.

Flucelvax Tetra may contain traces of beta-propiolactone, cetyltrimethylammonium bromide, and polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in pre-filled syringe (injection).
Clear to slightly opalescent liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of influenza in adults and children from 2 years of age.

Flucelvax Tetra should be used in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Adults and children from 2 years of age:

Age Group	Dose	Schedule
2 to < 9 years	One or two[a] 0.5 mL doses	If 2 doses, administer at least 4 weeks apart
9 years of age and older	One 0.5 mL dose	Not applicable

[a] Children less than 9 years of age who have not been previously vaccinated against influenza, should receive a second dose.

The safety and efficacy of Flucelvax Tetra in children from birth to less than 2 years of age has not been established.

Method of administration

For intramuscular injection only.
The preferred site for injection is the deltoid muscle of the upper arm. Young children with insufficient deltoid mass should be vaccinated in the anterolateral aspect of the thigh.

The vaccine must not be injected intravenously, subcutaneously or intradermally and must not be mixed with other vaccines in the same syringe.

For instructions on the handling of the vaccine before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, to any of the excipients listed in section 6.1, or to possible trace residues such as beta-propiolactone, cetyltrimethylammonium bromide, and polysorbate 80.

4.4 Special warnings and precautions for use

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

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

Vaccination should be postponed in patients with acute febrile illness until the fever is resolved.

As with all injectable vaccines, Flucelvax Tetra must be administered with caution to individuals with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient to prevent influenza.

A protective immune response may not be elicited in all vaccine recipients.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Flucelvax Tetra. There are no data available on co-administration of Flucelvax Tetra with other vaccines. Based on clinical experience with cell-based trivalent influenza vaccine (TIVc), Flucelvax Tetra can be given at the same time as other vaccines.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited data from the use of Flucelvax Tetra in pregnant women. However, inactivated influenza vaccines can be used in all stages of pregnancy. For egg-derived influenza vaccines larger datasets on safety are available for the second and third trimester, compared with the first trimester; however, data from worldwide use of influenza vaccine do not indicate any adverse foetal and maternal outcomes attributable to the vaccine.

There are no reproductive and developmental toxicology studies with Flucelvax Tetra. Reproductive and developmental toxicology data from cell-based trivalent influenza vaccine (TIVc) do not predict an increased risk of developmental abnormalities.

Breast-feeding
It is unknown whether Flucelvax Tetra is excreted in human milk. No effects on breast fed newborn/infant are anticipated. Flucelvax Tetra may be used during lactation.

Fertility
No human fertility data are available. Animal data, with cell-based trivalent influenza vaccine (TIVc), have not shown effects on female fertility. Male fertility has not been assessed in animals.

4.7 Effects on ability to drive and use machines

Flucelvax Tetra has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of Flucelvax Tetra in adults 18 years and older was evaluated in a randomised, controlled study (V130_01), in which 1334 subjects received Flucelvax Tetra. Similar rates of solicited local and systemic adverse reactions were reported in subjects who received Flucelvax Tetra and cell-based trivalent influenza vaccine comparator in this clinical trial.

The most commonly reported (≥10%) reactions in subjects who received Flucelvax Tetra were pain at the injection site (34%), headache (14%), fatigue (14%), myalgia (14%), erythema (13%) and induration (10%).

The incidence of some adverse reactions were considerably lower among subjects ≥ 65 years of age when compared to subjects 18 to < 65 years of age (see table below).

Tabulated list of adverse reactions

Adverse reactions reported are listed according to the following frequency categories: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100), not known (cannot be estimated from the available data).

Table 1: Adverse reactions reported following vaccination in adults 18 years and older in clinical trials and post-marketing surveilance.

MedDRA System Organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Frequency not known[3]
Immune system disorders				Allergic or immediate hypersensitivity reactions, including anaphylactic shock
Metabolism and nutrition disorders		Loss of appetite		
Nervous system disorders	Headache[1]			Paraesthesia
Gastrointestinal disorders		Nausea, Diarrhoea, Vomiting[2]		
Skin and subcutaneous tissue disorders				Generalised skin reactions including pruritus, urticaria or non-specific rash
Musculoskeletal and connective tissue disorders	Myalgia[1]	Arthralgia		
General disorders and administration site conditions	Injection site pain, Fatigue[1], Erythema, Induration[1]	Ecchymosis, Chills	Fever (≥ 38°C)	Extensive swelling of injected limb

[1] Reported as Common in the elderly population 65 years of age and older
[2] Reported as Uncommon in the elderly population 65 years of age and older
[3] Adverse reactions reported from post-marketing surveillance

Paediatric population (2 to less than 18 years of age)

The safety of Flucelvax Tetra in children 2 to less than 18 years of age has been evaluated in two clinical studies, V130_03 and V130_12. In the randomised, controlled study V130_03, 1159 paediatric subjects received Flucelvax Tetra (584 subjects 9 to <18 years; 575 subjects 4 to <9 years). Children 9 to less than 18 years of age received a single dose of Flucelvax Tetra. Children 4 to less than 9 years of age received one or two doses (separated by 4 weeks) of Flucelvax Tetra based on determination of the subject's prior influenza vaccination history. In this age group, 235 paediatric subjects received one dose and 340 subjects received two doses. Similar rates of solicited local and systemic adverse reactions were reported in subjects who received Flucelvax Tetra and cell-based trivalent influenza vaccine comparator in this clinical trial.

In the multinational, randomised, observer-blind study V130_12, the safety population included a total of 2255 children 2 to less than 18 years of age who received Flucelvax Tetra (580 subjects 2 to < 6 years; 564 subjects 6 to < 9 years; 1111 subjects 9 to < 18 years). Children 9 to less than 18 years of age received a single dose of Flucelvax Tetra. Children 2 to less than 9 years of age received one or two doses (separated by 28 days) of Flucelvax Tetra based on determination of the subject's prior influenza vaccination history.

The most common local and systemic adverse reactions reported in either study is described below by paediatric sub-group.

The most common (≥10%) local and systemic adverse reactions after one dose reported in paediatric subjects of 9 to < 18 years of age were injection site pain (58%), headache (22%), erythema (19%), fatigue (18%), myalgia (16%), and induration (15%).

The most common (≥10%) local and systemic adverse reactions after any vaccination in children 6 to less than 9 years of age were pain at the injection site (61%), injection site erythema (25%), injection site induration (19%), fatigue (16%), headache (16%) and injection site ecchymosis (11%).

The most common (≥10%) local and systemic adverse reactions after any vaccination in children 2 to less than 6 years of age were tenderness at the injection site (54%), injection site erythema (23%), sleepiness (21%), irritability (19%), injection site induration (15%), change in eating habits (14%) and injection site ecchymosis (11%).

Compared to adults 18 years of age and older, paediatric subjects generally reported higher rates of local and systemic adverse reactions.

In children who received a second dose of Flucelvax Tetra the incidence of adverse reactions following the second dose of vaccine was similar or slightly lower to that observed with the first dose.

The frequency of adverse reactions in children 2 to less and 18 years of age in these clinical studies are described in Table 2 below.

Table 2: Solicited adverse reactions reported in clinical studies in children 2 to < 18 years of age

MedDRA System Organ class	**Adverse Reactions**	**Frequency**		
		2 to < 9 years		**9 to < 18 years**
		2 to < 6 [1]	**6 to <9**	
Metabolism and nutrition disorders	Loss of appetite	N/A	Very common	Common
Nervous system disorders	Headache	N/A	Very common	Very common
Gastrointestinal disorders	Diarrhoea	Common	Common	Common
	Nausea	N/A	Common	Common
	Vomiting	Common	Common	Common
Musculoskeletal and connective tissue disorders	Myalgia [2]	N/A	Very common	Very common
	Arthralgia	N/A	Common	Common
General disorders and administration site conditions	Injection site tenderness	Very common	N/A	N/A
	Injection site pain	N/A	Very common	Very common
	Injection site erythema	Very common	Very common	Very common
	Injections site induration	Very common	Very common	Very common
	Injection site ecchymosis	Very common	Very Common	Common
	Sleepiness	Very common	N/A	N/A
	Irritability	Very common	N/A	N/A
	Fatigue	N/A	Very common	Very common
	Change in eating habits	Very common	N/A	N/A
	Chills/Shivering	Common	Common	Common
	Fever (≥38° C)	Common	Common	Common

[1] The youngest age range in study V130_03 was 4 to < 6 years

[2] Myalgia reported with a frequency of Common (3% and 6%) in children 6 to < 9 and 9 to < 18 years, respectively, in study V130_12

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 are no data for overdose with Flucelvax Tetra.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccine, ATC code: J07BB02

Mechanism of action

Flucelvax Tetra provides active immunisation against four influenza virus strains (two A subtypes and two B types) contained in the vaccine. Flucelvax Tetra induces humoral antibodies against the haemagglutinins. These antibodies neutralise influenza viruses.

Flucelvax Tetra is manufactured using Madin Darby Canine Kidney (MDCK) cells.

Specific levels of haemagglutination inhibition (HI) antibody titres post-vaccination with inactivated influenza vaccine have not been correlated with protection from influenza virus. In some human studies, antibody titres of 1:40 or greater have been associated with protection from influenza illness in up to 50% of subjects.

Antibody against one influenza virus type or subtype confers limited or no protection against another. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype.

Annual revaccination with current influenza vaccines is recommended because immunity declines during the year after vaccination and circulating strains of influenza virus may change from year to year.

Pharmacodynamic effects

Immunogenicity of Flucelvax Tetra in Adults 18 years of age and older

Immunogenicity of Flucelvax Tetra was evaluated in adults 18 years of age and older in a randomised, double-blind, controlled study (V130_01). In this study, subjects received Flucelvax Tetra (N = 1334) or one of the two formulations of comparator cell-based trivalent influenza vaccine (TIVc) [TIV1c (N = 677) or TIV2c (N = 669)]. The immune response to each of the vaccine antigens was assessed, 21 days after vaccination.

The immunogenicity endpoints were geometric mean antibody titres (GMTs) of haemagglutination inhibition (HI) antibodies response and percentage of subjects who achieved seroconversions, defined as a pre-vaccination HI titre of <1:10 with a post vaccination titre ≥1:40 or with a pre-vaccination HI titre of ≥10 and a minimum 4-fold increase in serum HI antibody titre.

Flucelvax Tetra was non-inferior to TIVc. Non-inferiority was established for all 4 influenza strains included in Flucelvax Tetra, as assessed by ratios of GMTs and the differences in the percentages of subjects achieving seroconversion at 3 weeks following vaccination. The antibody response to influenza B strains contained in Flucelvax Tetra was superior to the antibody response after vaccination with TIVc containing an influenza B strain from the alternate lineage. There was no evidence that the addition of the second influenza B strain resulted in immune interference to other strains included in the vaccine.

Age subgroup analyses in subjects 18 to less than 65 years of age and 65 years of age and above confirmed that HI antibody responses (GMT and differences in vaccine group seroconversion rates) met non-inferiority immunogenicity criteria 3 weeks following vaccination for all 4 influenza strains in both age groups.

The non-inferiority data observed are summarised in Table 3.

Table 3: Noninferiority of Flucelvax Tetra relative to TIVc in adults 18 years of age and above – Per protocol analysis set (V130_01)

		Flucelvax Tetra N = 1250	**TIV1c/TIV2c[a] N = 635/N = 639**	**Vaccine Group Ratio (95% CI)**	**Vaccine Group Difference (95% CI)**
A/H1N1	GMT (95% CI)	302.8 (281.8-325.5)	298.9 (270.3-330.5)	1.0 (0.9-**1.1**)	-
	Seroconversion Rate[b] (95% CI)	49.2% (46.4-52.0)	48.7% (44.7-52.6)	-	-0.5% (-5.3-**4.2**)
A/H3N2	GMT (95% CI)	372.3 (349.2-396.9)	378.4 (345.1-414.8)	1.0 (0.9-**1.1**)	-
	Seroconversion Rate[b] (95% CI)	38.3% (35.6-41.1)	35.6% (31.9-39.5)	-	-2.7% (-7.2-**1.9**)
B1	GMT (95% CI)	133.2 (125.3-141.7)	115.6 (106.4-125.6)	0.9 (0.8-**1.0**)	-
	Seroconversion Rate[b] (95% CI)	36.6% (33.9-39.3)	34.8% (31.1-38.7)	-	-1.8% (-6.2-**2.8**)
B2	GMT (95% CI)	177.2 (167.6-187.5)	164.0 (151.4-177.7)	0.9 (0.9-**1.0**)	-
	Seroconversion Rate[b] (95% CI)	39.8% (37.0-42.5)	35.4% (31.7-39.2)	-	-4.4% (-8.9-**0.2**)

Abbreviations: GMT = geometric mean titre; CI = confidence interval.
[a] The comparator vaccine for noninferiority comparisons for A/H1N1, A/H3N2 and B1 is TIV1c, for B2 it is TIV2c.
[b] Seroconversion rate = percentage of subjects with either a pre-vaccination HI titre <1:10 and post-vaccination HI titre ≥1:40 or with a pre-vaccination HI titre ≥1:10 and a minimum 4-fold increase in post-vaccination HI antibody titre.
Bold = Non-inferiority criterion met.

Clinical efficacy of cell-based trivalent influenza vaccine (TIVc) against culture-confirmed influenza in adults

The efficacy experience with TIVc is relevant to Flucelvax Tetra because both vaccines are manufactured using the same process and have overlapping compositions.

A multinational, randomised, observer-blinded, placebo-controlled trial (V58P13) was performed to assess clinical efficacy and safety of TIVc during the 2007-2008 influenza season in adults aged 18 to less than 50 years. A total of 11,404 subjects were enrolled to receive TIVc (N = 3828), Agrippal (N = 3676) or placebo (N = 3900) in a 1:1:1 ratio.

TIVc efficacy was defined as the prevention of culture-confirmed symptomatic influenza illness caused by viruses antigenically matched to those in the vaccine compared to placebo. Influenza cases were identified by active and passive surveillance of influenza-like illness (ILI). ILI was defined

according to Centers for Disease Control and Prevention (CDC) case definition, i.e., a fever (oral temperature ≥100.0°F / 38°C) and cough or sore throat. After an episode of ILI, nose and throat swab samples were collected for analysis. Vaccine efficacies against vaccine-matched influenza viral strains, against all influenza viral strains, and against individual influenza viral subtypes were calculated (Table 4).

Table 4: Comparative efficacy of TIVc versus placebo against culture-confirmed influenza by influenza viral subtype (V58P13)

		TIVc (N = 3776)		Placebo (N = 3843)		Vaccine Efficacy*	
		Attack Rate (%)	Number of Subjects with Influenza	Attack Rate (%)	Number of Subjects with Influenza	%	Lower Limit of One-Sided 97.5% CI
Antigenically Matched Strains							
Overall		**0.19**	**7**	**1.14**	**44**	**83.8**	**61.0**
Individual strains	**A/H3N2****	0.05	2	0	0	--	--
	A/H1N1	0.13	5	1.12	43	88.2	67.4
	B**	0	0	0.03	1	--	--
All Culture-Confirmed Influenza							
Overall		**1.11**	**42**	**3.64**	**140**	**69.5**	**55.0**
Individual strains	**A/H3N2**	0.16	6	0.65	25	75.6	35.1
	A/H1N1	0.16	6	1.48	57	89.3	73.0
	B	0.79	30	1.59	61	49.9	18.2

* Simultaneous one-sided 97.5% confidence intervals for the vaccine efficacy of each influenza vaccine relative to placebo based on the Sidak-corrected score confidence intervals for the two relative risks. Vaccine Efficacy = (1 - Relative Risk) x 100%;

** There were too few cases of influenza due to vaccine-matched influenza A/H3N2 or B to adequately assess vaccine efficacy.

Paediatric population

Immunogenicity of Flucelvax Tetra in Children and Adolescents 4 to less than 18 Years of Age

Immunogenicity of Flucelvax Tetra was evaluated in children 4 to less than 18 years of age as part of a randomised, double-blind, controlled study (V130_03). In this study, subjects received Flucelvax Tetra (N = 1159) or one of the two formulations of comparator cell-based trivalent influenza vaccine (TIVc) [TIV1c (N = 593), or TIV2c (N = 580)]. The immune response to each of the vaccine antigens was assessed 21 days after vaccination.

The immunogenicity endpoints were GMTs of HI antibodies response and percentage of subjects who achieved seroconversions (seroconversion rate), defined as a pre-vaccination HI titre of <1:10 with a post-vaccination titre ≥1:40 or with a pre-vaccination HI titre ≥ 1:10 and a minimum 4-fold increase in serum HI antibody titre.

Flucelvax Tetra was noninferior to TIVc in children 4 to less than 18 years of age. Non-inferiority was established for all 4 influenza strains included in the Flucelvax Tetra, as assessed by ratios of GMTs and the differences in the percentages of subjects achieving seroconversion at 3 weeks following vaccination. The antibody response to influenza B strains contained in Flucelvax Tetra was superior to the antibody response after vaccination with TIVc containing an influenza B strain from the alternate lineage. There was no evidence that the addition of the second B strain resulted in immune interference to other strains included in the vaccine.

The immunogenicity data in subjects 4 to less than 18 years of age are summarised in Table 5.

Table 5: GMTs and seroconversion rates (with 95% CI) in subjects 4 to <18 years of age, 3 weeks after vaccination with Flucelvax Tetra or TIV1c/TIV2c - Per Protocol Set (V130_03)

		Flucelvax Tetra	TIV1c/TIV2c[a]
A/H1N1		N = 1014	N = 510
	GMT (95% CI)	1090 (1027-1157)	1125 (1034-1224)
	Seroconversion Rate[b]	**72%** (69-75)	**75%** (70-78)
A/H3N2		N = 1013	N = 510
	GMT (95% CI)	738 (703-774)	776 (725-831)
	Seroconversion Rate[b]	**47%** (44-50)	**51%** (46-55)
B1		N = 1013	N = 510
	GMT (95% CI)	155 (146-165)	154 (141-168)
	Seroconversion Rate[b]	**66%** (63-69)	**66%** (62-70)
B2		N = 1009	N = 501
	GMT (95% CI)	185 (171-200)	185 (166-207)
	Seroconversion Rate[b]	**73%** (70-76)	**71%** (67-75)

[a] For H1N1, H3N2 and B1 influenza strains TIV1c data are presented, whereas for B2 influenza strain TIV2c data are presented.

[b] Seroconversion rate = percentage of subjects with either a pre-vaccination HI titre <1:10 and post-vaccination HI titre ≥1:40 or with a pre-vaccination HI titre ≥1:10 and a minimum 4-fold increase in post-vaccination HI antibody titre.

Bold- CHMP immunogenicity criteria met. The percentage of subjects with seroconversion or significant increase in HI antibody titre is >40%, the percentage of subjects achieving an HI titre ≥1:40 is >70%.

Clinical efficacy of Flucelvax Tetra in the paediatric population 2 to less than 18 years of age

Absolute efficacy of Flucelvax Tetra was evaluated in children 2 to less than 18 years of age in Study V130_12. This was a multinational, randomised, non-influenza vaccine comparator-controlled efficacy study conducted in 8 countries over 3 influenza seasons, in which 4514 subjects were enrolled to received 0.5 ml of Flucelvax Tetra or a non-influenza comparator in a 1:1 ratio. Based on influenza vaccination history, participants received one or two doses (28 days apart) of the study vaccine.

Flucelvax Tetra efficacy was assessed by the prevention of confirmed influenza illness caused by any influenza Type A or B strain. Influenza cases were identified by active surveillance of influenza-like illness (ILI) and confirmed by viral culture and/or real-time polymerase chain reaction (RT-PCR). An ILI episode was defined as a fever body temperature ≥ 37.8°C) along with at least one of the following: cough, sore throat, nasal congestion, or rhinorrhoea. Vaccine efficacy against laboratory confirmed influenza was calculated (Table 6).

Table 6: Number of Subjects with First-Occurrence RT-PCR Confirmed or Culture Confirmed Influenza and Absolute Vaccine Efficacy (95% CI), in Subjects 2 to less than 18 Years of Age– FAS Efficacy[1] (Study V130_12)

	Number of subjects per protocol[1]	Number of cases of influenza	Attack Rate (%)	Vaccine Efficacy (VE)	
				%	95% CI of VE
RT-PCR or Culture Confirmed Influenza					
Flucelvax Tetra	2257	175	7.8	54.63	45.67, 62.12
Non-Influenza Comparator	2252	364	16.2	-	-
Culture Confirmed Influenza					
Flucelvax Tetra	2257	115	5.1	60.81	51.30, 68.46
Non-Influenza Comparator	2252	279	12.4	-	-
Antigenically Matched Culture-Confirmed Influenza					
Flucelvax Tetra	2257	90	4.0	63.64	53.64, 71.48
Non-Influenza Comparator	2252	236	10.5	-	-

[1]Number of subjects in the Full-Analysis Set (FAS)– Efficacy, which included all subjects randomised, received a study vaccination and provided efficacy data.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity and toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

12 months

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
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 suspension in pre-filled syringes (type I glass), with a plunger stopper (bromobutyl rubber), with or without needle.

Pack of 1 pre-filled syringe, with needle
Pack of 10 pre-filled syringes, with or without needles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Shake before use. After shaking, the normal appearance of the vaccine is a clear to slightly opalescent 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 is observed, do not administer the vaccine.

Any unused medicinal product or 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/1/18/1326/001
EU/1/18/1326/002
EU/1/18/1326/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 December 2018

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

Name and address of the manufacturer(s) of the biological active substance(s)
Seqirus Inc.
475 Green Oaks Parkway
Holly Springs
NC 27540
United States

Name and address of the manufacturer(s) responsible for batch release
Seqirus Vaccines Ltd
Gaskill Road
Speke
Liverpool
L24 9GR
United Kingdom

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

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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**

The requirements for submission of periodic safety update reports 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 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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Carton box for syringe(s) with needle:
- 1 pre-filled syringe (0.5 ml) with needle
- 10 pre-filled syringes (0.5 ml) with needle
Carton box for syringe(s) without needle:
- 10 pre-filled syringes (0.5 ml) without needle

1. NAME OF THE MEDICINAL PRODUCT

Flucelvax Tetra suspension for injection in pre-filled syringe
Influenza vaccine (surface antigen, inactivated, prepared in cell cultures)
2019/2020 season

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Influenza virus surface antigens (haemagglutinin and neuraminidase), inactivated, of the following strains*:

A/Brisbane/02/2018 (H1N1)pdm09 - like strain (A/Idaho/07/2018) 15 micrograms HA**

A/Kansas/14/2017 (H3N2) - like strain (A/Indiana/08/2018) 15 micrograms HA**

B/Colorado/06/2017 - like strain (B/Iowa/06/2017) 15 micrograms HA**

B/Phuket/3073/2013 - like strain (B/Singapore/INFTT-16-0610/2016) 15 micrograms HA**

per 0.5 ml dose
…….
* propagated in Madin Darby Canine Kidney (MDCK) cells
** haemagglutinin

3. LIST OF EXCIPIENTS

Sodium chloride, potassium chloride, magnesium chloride hexahydrate, disodium phosphate dihydrate, potassium dihydrogen phosphate and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in pre-filled syringe

10 pre-filled syringes (0.5 ml) without needle
1 pre-filled syringe (0.5 ml) with needle
10 pre-filled syringes (0.5 ml) with needle

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
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/1/18/1326/001 10 pre-filled syringes without needle
EU/1/18/1326/002 1 pre-filled syringe with needle
EU/1/18/1326/003 10 pre-filled syringes with needle

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

Shake before 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

Pre-filled syringe label

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

Flucelvax Tetra injection
Influenza vaccine
2019/2020 season

2. METHOD OF ADMINISTRATION

i.m.

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

Flucelvax Tetra - suspension for injection in pre-filled syringe
Influenza vaccine (surface antigen, inactivated, 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 medicine 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 Flucelvax Tetra is and what it is used for

Flucelvax Tetra is a vaccine against flu (influenza). Flucelvax Tetra is prepared in cell cultures, and, therefore, is egg-free.
When a person is given the vaccine, the immune system (the body's natural defence system) will produce its own protection against the influenza virus. None of the ingredients in the vaccine can cause flu.

Flucelvax Tetra is used to prevent flu in adults and children from 2 years of age.

The vaccine targets four strains of influenza virus following the recommendations by the World Health Organisation for the 2019/2020 season.

2. What you need to know before you receive Flucelvax Tetra

You should not receive Flucelvax Tetra:
If you are allergic to:
- the active ingredients or any of the other ingredients of this medicine (listed in section 6)
- beta-propiolactone, cetyltrimethylammonium bromide, or polysorbate 80, which are trace residues from the manufacturing process.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before receiving Flucelvax Tetra.

BEFORE receiving the 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) following the administration. This reaction may occur with Flucelvax Tetra as with all vaccines that are injected.
- You should tell your doctor if you have an acute illness associated with fever. Your doctor may decide to delay your vaccination until your fever is gone.
- You should tell your doctor if your immune system is impaired, or if you are undergoing treatment which affects the immune system, e.g. with medicine against cancer (chemotherapy) or corticosteroid medicines (see section "Other medicines and Flucelvax Tetra").
- You should tell your doctor if you have a bleeding problem or bruise easily.
- Fainting can occur following, or even before, any needle injection, therefore tell the doctor or nurse if you fainted with a previous injection.

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

Other medicines and Flucelvax Tetra
Tell your doctor or nurse if you are using, have recently used or might use any other medicines, including medicines obtained without a prescription or if you have recently received any other vaccine.

Flucelvax Tetra may be given at the same time as other vaccines.

Pregnancy and breast-feeding
Pregnancy:
Tell your doctor if you are pregnant, think you may be pregnant or are planning to have a baby. Influenza vaccinations can be used at any stage of pregnancy.

Breast-feeding:
Use of Flucelvax Tetra during breast-feeding has not been studied. Flucelvax Tetra may be used during breast-feeding.

Driving and using machines
Flucelvax Tetra has no or negligible effect on your ability to drive and use machines.

Flucelvax Tetra contains sodium chloride and potassium chloride
This vaccine contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium free'.
This vaccine contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially 'potassium free'.

3. How Flucelvax Tetra is given

Flucelvax Tetra is given to you by your doctor or nurse as an injection into the muscle at the top of the upper arm (deltoid muscle).

Adults and children from 2 years of age:

One dose of 0.5 ml

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
The following side effects have been reported during clinical trials and during general use:

Very serious side effects
Tell your doctor immediately or go to the casualty department at your nearest hospital if you experience the following side effect – you may need urgent medical attention or hospitalisation:

- difficulty in breathing, dizziness, a weak and rapid pulse and skin rash which are symptoms of an anaphylactic reaction (a very severe allergic reaction)

Serious side effects
Tell your doctor immediately if you experience any of the following side effects – you may need medical attention:

- Extensive swelling of injected limb

Mild side effects
Very common (may affect more than 1 in 10 people):
- Injection site pain, bruising, reddening and hardening or swelling at the site of the injection
- Headache
- Muscle pain
- Tiredness
- Loss of appetite
- Irritability (only reported in children from 2 to < 6 years)
- Sleepiness (only reported in children 2 to < 6 years)

Hardening or swelling at the site of the injection, headache, muscle pain, and tiredness were common in the elderly.
Bruising at the site of the injection was common in adults, eldery and children 9 to < 18 years
Headache was common in the elderly
Loss of appetite was common in adults, eldery and children 9 to < 18 years

Common (may affect up to 1 in 10 people):
- Nausea, vomiting, diarrhoea
- Joint pain
- Shivering
- Change in eating habits (only reported in children from 2 to < 6 years)
- Fever (≥ 38°C)

Vomiting was uncommon in the elderly.
Fever was uncommon in adults and the elderly

Not known (cannot be estimated from the available data):
- Numbness and tingling sensation
- Generalised skin reactions including itching, bumps on the skin or non-specific rash

Reporting of side effects
If you get any side effects, talk to your healthcare professional. 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 Flucelvax Tetra

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

Store in a refrigerator (2 °C to 8 °C). Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.

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

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

6. Contents of the pack and other information

What Flucelvax Tetra contains

The active substances are influenza virus surface antigens (haemagglutinin and neuraminidase), inactivated, of the following strains*:

A/Brisbane/02/2018 (H1N1)pdm09 - like strain (A/Idaho/07/2018) 15 micrograms HA**

A/Kansas/14/2017 (H3N2) - like strain (A/Indiana/08/2018) 15 micrograms HA**

B/Colorado/06/2017 - like strain (B/Iowa/06/2017) 15 micrograms HA**

B/Phuket/3073/2013 - like strain (B/Singapore/INFTT-16-0610/2016) 15 micrograms HA**

per 0.5 ml dose
…….
* propagated in Madin Darby Canine Kidney (MDCK) cells (this is the special cell culture in which the influenza virus is grown);
** haemagglutinin

This vaccine complies with the World Health Organisation (WHO) recommendation (northern hemisphere) and EU recommendation for the 2019/2020 season.

The other ingredients are: sodium chloride, potassium chloride, magnesium chloride hexahydrate, disodium phosphate dihydrate, potassium dihydrogen phosphate and water for injections.

What Flucelvax Tetra looks like and contents of the pack

Flucelvax Tetra is a suspension for injection in a pre-filled syringe (ready to use syringe).
Flucelvax Tetra is a clear to slightly opalescent suspension.
A single syringe contains 0.5 ml of suspension for injection.
Flucelvax Tetra is available in packs containing 1 pre-filled syringe with needle or 10 pre-filled syringes with or without needles.
Not all pack sizes may be marketed.

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

Manufacturer
Seqirus Vaccines Limited
Gaskill Road, Speke
L24 9GR Liverpool
United Kingdom

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

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

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Seqirus Netherlands B.V.Nederland/Netherlands	Seqirus Netherlands B.V. Nyderlandai

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Österreich
Valneva Austria GmbH, Wien
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România
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Slovenija
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Slovenská republika
Seqirus Netherlands B.V. Holandsko
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Suomi/Finland
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United Kingdom
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This leaflet was last revised in.

Other sources of information

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

Shake before use. After shaking, the normal appearance of the vaccine is a clear to slightly opalescent 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.