ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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/Wisconsin/67/2022 (H1N1)pdm09-like strain (A/Georgia/12/2022, CVR-167) 15 micrograms HA**

A/Massachusetts/18/2022 (H3N2)-like strain (A/Sydney/1304/2022, wild type) 15 micrograms HA**

B/Austria/1359417/2021-like strain (B/Singapore/WUH4618/2021, wild type) 15 micrograms HA**

B/Phuket/3073/2013-like strain (B/Singapore/INFTT-16-0610/2016, wild type) 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 2024/2025 SEASON.

Flucelvax Tetra may contain traces of beta-propiolactone, cetyltrimethylammonium bromide, and polysorbate 80 (see section 4.3).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection (injection)
Clear to slightly opalescent liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of influenza in adults and children from 6 months of age.

Flucelvax Tetra should be used in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Age group	Dose	Schedule
6 months 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.

Children below 6 months of age
The safety and efficacy of Flucelvax Tetra in children from birth to less than 6 months of age has not been established. No data are available.

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.

Hypersensitivity and anaphylaxis

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

Concurrent illness

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

Thrombocytopenia and coagulation disorders

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.

General

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.

Excipients with known effect

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

Potassium
This vaccine contains potassium, less than 1 mmol (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 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

Inactivated influenza vaccines, such as Flucelvax Tetra, can be given in any stage of pregnancy. Larger safety datasets are available on vaccine use during the second or third trimester, compared with the first trimester; however, data from worldwide use of influenza vaccines do not indicate any adverse foetal and maternal outcomes attributable to the vaccine.

A prospective Pregnancy Exposure Registry was conducted in the United States (US) and data were collected from 665 women vaccinated with Flucelvax Tetra during 3 Northern Hemisphere influenza seasons (2017-18 to 2019-20), of whom 28% were exposed during their first trimester. Based on pregnancy outcomes and predefined infant safety outcomes, there was no evidence of adverse foetal, newborn or pregnancy outcomes attributable to the vaccine during any stage of pregnancy.

There have been 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 breastfed newborn/infant are anticipated. Flucelvax Tetra may be given 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 1 334 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 study.

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 studies 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, Guillain-Barre Syndrome
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 (6 months to less than 18 years of age)

The safety of Flucelvax Tetra in children 6 months to less than 18 years of age has been evaluated in three clinical studies, V130_03, V130_12 and V130_14. In the randomised, controlled study V130_03, 1 159 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 study.

In the multinational, randomised, observer-blind study V130_12, the safety population included a total of 2 255 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; 1 111 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.

In the multinational, randomised, observer blind study V130_14, the safety population included a total of 5 697 subjects 6 months to less than 4 years of age of whom N=2 856 received Flucelvax Tetra. Children 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 across any paediatric study is described below by sub-group.

The most common (≥10%) local and systemic adverse reactions after any vaccination in children 6 to less than 18 years of age were pain at the injection site (61%), injection site erythema (25%), injection site induration (19%), fatigue (18%), headache (22%) myalgia (16%), injection site ecchymosis (11%) and loss of appetite (10%).

The most common (≥10%) local and systemic adverse reactions after any vaccination in children 6 months to less than 6 years of age were tenderness at the injection site (54%), injection site erythema (23%), sleepiness (21%), irritability (21%), injection site induration (15%), change in eating habits (16%), diarrhoea (13%), injection site ecchymosis (11%) and fever (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 highest frequency of adverse reactions in children 6 months 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 6 months to < 18 years of age

MedDRA system organ class	Very Common	Common
6 months to < 6 years[1]		
Gastrointestinal disorders	Diarrhoea	Vomiting
General disorders and administration site conditions	Injection site tenderness, injection site erythema, injection site induration injection site ecchymosis, sleepiness irritability, change in eating habits, fever (≥38° C)[2]	Chills/Shivering
6 to < 18 years[3]		
Metabolism and nutrition disorders	Loss of appetite	
Nervous system disorders	Headache	
Gastrointestinal disorders		Nausea
Musculoskeletal and connective tissue disorders	Myalgia[4]	Arthralgia
General disorders and administration site conditions	Injection site pain, injection site erythema, injection site induration injection site ecchymosis, fatigue	Chills/Shivering, fever (≥38° C)

[1] Frequency categories based on the highest rates from the overlapping age groups in the following 3 studies: V130_14 (6 months to < 4 years); V130_12 (2 to < 6 years); V130_03 (4 to < 6 years)

[2] Fever reported as common in V130_12 and V130_03 and very common in V130_14

[3] Frequency categories based on the highest rates from the following 2 studies: V130_03 (6 to < 18 years) and V130_12 (6 to < 18 years)

[4] Myalgia reported as common in V130_12 and very common in V130_03

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. 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

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: Non-inferiority 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 study (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 = 1 159) 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%

Clinical efficacy of Flucelvax Tetra in the paediatric population 6 months to less than 18 years of age

Absolute efficacy of Flucelvax Tetra in the paediatric population was evaluated in two clinical studies. Efficacy in children 2 to less than 18 years of age was evaluated 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 4 514 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.

Efficacy in children 6 months to less than 4 years was evaluated in Study V130_14. This was a multinational, randomised, observer-blind, non-influenza vaccine comparator-controlled efficacy study conducted in 15 countries over 5 influenza seasons, in which 5 697 subjects received either 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 real-time polymerase chain reaction (RT-PCR) and viral culture. An ILI episode was defined as a fever body temperature ≥ 37.8°C with at least one of the following on the same day: cough, sore throat, nasal congestion, rhinorrhoea, earache or ear discharge. Vaccine efficacy against laboratory confirmed influenza was calculated (Table 7).

Table 7: Number of subjects with first-occurrence RT-PCR confirmed influenza, culture-confirmed any strain and antigenically matched influenza and absolute vaccine efficacy, in subjects 6 months to less than 4 years of age – FAS efficacy[1] (Study V130_14)

	Number of subjects per protocol	Number of cases of influenza	Attack rate (%)	Vaccine efficacy (VE)	
				%	Lower Limit of Two Sided CI of VE
RT-PCR confirmed influenza[2, 3]					
Flucelvax Tetra	2856	104	3.64	41.26	21.55[4]
Non-Influenza comparator	2835	173	6.10	-	-
Culture-confirmed influenza[5]					
Flucelvax Tetra	2856	61	2.14	50.67	32.83
Non-Influenza comparator	2835	121	4.27	-	-
Antigenically matched culture-confirmed influenza[2]					
Flucelvax Tetra	2856	44	1.54	46.90	19.19[6]
Non-Influenza Comparator	2835	82	2.89	-	-

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

[2] Primary endpoint of study

[3] The number of subjects with first occurrence of moderate-to-severe RT-PCR confirmed influenza was 9 in the comparator group and 0 in the Flucelvax Tetra group.

[4] The pre-defined success criterion was defined as the lower limit of the two-sided 97.98% CI of absolute vaccine efficacy was above 0%

[5] Culture confirmed influenza due to any influenza Type A and/or Type B virus regardless of antigenic match to the influenza strains in the vaccine (two-sided 95% CI)

[6] The pre-defined success criterion was defined as the lower limit of the two-sided 97.5% CI of absolute vaccine efficacy was above 0%

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

1 year

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 or without 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

The vaccine comes ready to use. 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
EU/1/18/1326/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 December 2018
Date of latest renewal:

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 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 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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Flucelvax Tetra suspension for injection in pre-filled syringe
Influenza vaccine (surface antigen, inactivated, prepared in cell cultures)
2024/2025 SEASON

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

A/Wisconsin/67/2022 (H1N1)pdm09-like strain 15 micrograms HA**

A/Massachusetts/18/2022 (H3N2)-like strain 15 micrograms HA**

B/Austria/1359417/2021-like strain 15 micrograms HA**

B/Phuket/3073/2013-like strain 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

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
1 pre-filled syringe (0.5 ml) without needle

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.

Read the package leaflet before use.
Shake before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
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
EU/1/18/1326/004 1 pre filled syringe without needle

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

Pre-filled syringe label

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

Flucelvax Tetra injection
Influenza vaccine
2024/2025 Season

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

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

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 6 months of age.

The vaccine targets four strains of influenza virus following the recommendations by the World Health Organisation for the 2024/2025 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.

<u>BEFORE receiving the vaccine</u>
- 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.

Children aged less than 6 months
This 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 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 vaccines may be given in any trimester of pregnancy.

Breast-feeding
Use of Flucelvax Tetra during breast-feeding has not been studied. No effects on breast fed babies are expected. Flucelvax Tetra may be given 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 and potassium
This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say 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) or into the muscle of the upper and outer part of the thigh in young children depending on the muscle size.

Adults and children from 6 months of age:

One dose of 0.5 ml

If your child is younger than 9 years of age and has not been previously vaccinated against flu, a second dose should be given after at least 4 weeks.

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 studies 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:

- You feel weak, you have difficulty moving around or you experience numbness or tingling in your limbs. These can be symptoms of Guillain-Barré syndrome (GBS), an autoimmune disease caused by your body's own immune system.
- Extensive swelling of injected limb

Other side effects
Very common (may affect more than 1 in 10 people)
- Injection site pain or tenderness, 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 6 months to < 6 years)
- Sleepiness (only reported in children 6 months to < 6 years)
- Change of eating habits (only reported in children from 6 months to < 6 years)
- Fever (≥ 38°C)
- Diarrhoea

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.
Fever was uncommon in adults and elderly and common in children from 4 to < 18 years

Common (may affect up to 1 in 10 people)
- Nausea, vomiting
- Joint pain
- Shivering

Vomiting was uncommon in the elderly.

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

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist 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 Flucelvax Tetra

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

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.

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 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 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/Wisconsin/67/2022 (H1N1)pdm09-like strain (A/Georgia/12/2022, CVR-167) 15 micrograms HA**

A/Massachusetts/18/2022 (H3N2)-like strain (A/Sydney/1304/2022, wild type) 15 micrograms HA**

B/Austria/1359417/2021-like strain (B/Singapore/WUH4618/2021, wild type) 15 micrograms HA**

B/Phuket/3073/2013-like strain (B/Singapore/INFTT-16-0610/2016, wild type) 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 2024/2025 Season.

The other ingredients are: sodium chloride, potassium chloride, magnesium chloride hexahydrate, disodium phosphate dihydrate, potassium dihydrogen phosphate and water for injections.
(see Section 2 – Flucelvax Tetra contains sodium and potassium)

What Flucelvax Tetra looks like and contents of the pack

Flucelvax Tetra is a suspension for injection (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 or without needle or 10 pre-filled syringes with or without needles.
Not all pack sizes may be marketed.

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

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

België/Belgique/Belgien
Seqirus Netherlands B.V.Nederland/Netherlands
Tel: +31 (0) 20 204 6900

България
Seqirus Netherlands B.V. Нидерландия
Тел.: +31 (0) 20 204 6900

Česká republika
Seqirus Netherlands B.V. Nizozemsko
Tel: +31 (0) 20 204 6900

Danmark
Seqirus Netherlands B.V. Holland
Tlf: +31 (0) 20 204 6900

Deutschland
Seqirus GmbH
Tel: 0800 360 10 10

Eesti
Seqirus Netherlands B.V. Holland
Tel: +31 (0) 20 204 6900

Ελλάδα
WIN MEDICA A.E.
Τηλ: +30 210 7488821

España
Seqirus Spain, S.L., Barcelona
Tel: 937 817 884

France
Seqirus Netherlands B.V. Netherlands
Tél: +31 (0) 20 204 6900

Hrvatska
Seqirus Netherlands B.V. Nizozemska
Tel: +31 (0) 20 204 6900

Ireland
Seqirus UK Limited Maidenhead
Tel: +44 1628 641 500

Ísland
Seqirus Netherlands B.V. Holland
Sími: +31 (0) 20 204 6900

Italia
Seqirus S.r.l. Siena
Tel: +39 0577 096400

Κύπρος
Seqirus Netherlands B.V. Ολλανδία
Τηλ: +31 (0) 20 204 6900

Lietuva
Seqirus Netherlands B.V. Nyderlandai
Tel: +31 (0) 20 204 6900

Luxembourg/Luxemburg
Seqirus Netherlands B.V. Netherlands
Tél/Tel: +31 (0) 20 204 6900

Magyarország
Seqirus Netherlands B.V. Hollandia
Tel.: +31 (0) 20 204 6900

Malta
Seqirus Netherlands B.V. In-Netherlands
Tel: +31 (0) 20 204 6900

Nederland
Seqirus Netherlands B.V. Amsterdam
Tel: +31 (0) 20 204 6900

Norge
Seqirus Netherlands B.V. Nederland
Tlf: +31 (0) 20 204 6900

Österreich
Valneva Austria GmbH, Wien
Tel: +43 1 20620 2020

Polska
Seqirus Netherlands B.V. Holandia
Tel.: +31 (0) 20 204 6900

Portugal
Seqirus Netherlands B.V. Países Baixos
Tel: +31 (0) 20 204 6900

România
Seqirus Netherlands B.V. Olanda
Tel: +31 (0) 20 204 6900

Slovenija
Seqirus Netherlands B.V. Nizozemska
Tel: +31 (0) 20 204 6900

Slovenská republika
Seqirus Netherlands B.V. Holandsko
Tel: +31 (0) 20 204 6900

Suomi/Finland
Seqirus Netherlands B.V. Alankomaat
Puh/Tel: +31 (0) 20 204 6900

Sverige
Seqirus Netherlands B.V. Nederländerna
Tel: +31 (0) 20 204 6900

Latvija
Seqirus Netherlands B.V. Nīderlande
Tel: +31 (0) 20 204 6900

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.