FLUARIX TETRA

Quadrivalent influenza vaccine (split virion, inactivated), suspension for injection

1. NAME OF THE MEDICINAL PRODUCT

Fluarix Tetra suspension for injection in pre-filled syringe
Influenza vaccine (split virion, inactivated)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluarix Tetra is an inactivated influenza vaccine (split virion), containing antigens (propagated in embryonated eggs) equivalent to the following strains:

A/Sydney/5/2021 (H1N1) pdm09 - like strain (A/Sydney/5/2021, IVR-229);

A/Darwin/9/2021 (H3N2) - like strain (A/Darwin/6/2021, IVR-227);

B/Austria/1359417/2021 - like strain (B/Austria/1359417/2021, BVR-26);

B/Phuket/3073/2013 - like strain (B/Phuket/3073/2013, wild type)

Each 0.5 ml vaccine dose contains 15 µg haemagglutinin of each of the recommended strains.

This vaccine complies with the World Health Organisation (WHO) recommendation (Southern Hemisphere) for the season **2023**.

For the full list of excipients, see *section 5.1.*

Fluarix Tetra may contain traces of Formaldehyde, Sodium Deoxycholate, Ovalbumin, Gentamicin Sulphate and Hydrocortisone. The maximum amount of Ovalbumin that may be present is not more than 0.05 micrograms per dose.

3. CLINICAL INFORMATION

3.1 Therapeutic indications

Fluarix Tetra is indicated for active immunisation of adults and children from 6 months of age for the prevention of influenza disease caused by the two influenza A virus subtypes and the two influenza B virus types contained in the vaccine (see *Pharmacodynamics*).

The use of Fluarix Tetra should be based on official recommendations.

3.2 Posology and method of administration

Posology

Fluarix Tetra should be administered as a single 0.5 ml injection.

Children 6 months to less than 9 years, who have not previously been vaccinated against influenza should receive a second dose of 0.5 ml after an interval of at least 4 weeks.

Children aged <6 months:
The safety and efficacy of Fluarix Tetra in children aged <6 months have not been established.

Vaccination should be carried out by intramuscular injection preferably into the deltoid muscle or anterolateral thigh (depending on the muscle mass).

Method of administration

Immunisation should be carried out by intramuscular injection.

Precautions to be taken before handling or administering the medicinal product.

For instructions for preparation of the medicinal product before administration, see *section 5.6.*

3.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in *section 5.1* or to any component that may be present as traces such as eggs (ovalbumin, chicken proteins), formaldehyde, gentamicin sulphate and sodium deoxycholate.

Immunisation should be postponed in patients with febrile illness or acute infection.

3.4 Special warnings and precautions for use

It is good clinical practice to precede vaccination by a review of the medical history (especially with regards to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.

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

Fluarix Tetra is not effective against all possible strains of influenza virus. Fluarix Tetra is intended to provide protection against those strains of virus from which the vaccine is prepared and to closely related strains.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

Fluarix Tetra should under no circumstances be administered intravascularly.

As with other vaccines administered intramuscularly, Fluarix Tetra should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects.

Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents 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.

Interference with serological testing. See *section 3.5.*

3.5 Interaction with other medicinal products and other forms of interaction

Fluarix Tetra can be administered to patients aged 50 years and over simultaneously with pneumococcal polysaccharide vaccines (see *Pharmacodynamics*).

Fluarix Tetra can be concomitantly administered with adjuvanted herpes zoster vaccine (Shingrix) (see *Pharmacodynamics*).

Incidence of fatigue, headache, myalgia, arthralgia, gastrointestinal symptoms (including nausea, vomiting, diarrhea and/or abdominal pain) and shivering reported in subjects vaccinated concomitantly with Fluarix Tetra and Shingrix is similar to that observed with Shingrix alone, and higher compared to Fluarix Tetra alone.

If Fluarix Tetra is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites (contralateral).

Following influenza vaccination, false-positive results in serology tests using the ELISA method to detect antibodies against HIV1, Hepatitis C and especially HTLV1 have been observed. The Western Blot technique disproves the false-positive ELISA test results. The transient false-positive reactions could be due to the IgM response by the vaccine.

3.6 Fertility, pregnancy and lactation

Pregnancy

Inactivated influenza vaccines can be used in all stages of pregnancy. Larger datasets on safety are available for the second and third trimester, compared with the first trimester; however, data from worldwide use of inactivated influenza vaccines do not indicate any adverse foetal and maternal outcomes attributable to the vaccine (see *Non-clinical Information*).

When administered during pregnancy, safety data on inactivated seasonal influenza vaccines based on systematic literature review, and available post-marketing data on Fluarix Tetra, do not indicate an increased risk of adverse pregnancy outcomes.

Breast-feeding

Fluarix Tetra may be used during breast-feeding.

Fertility

No fertility data are available.

3.7 Undesirable effects

Adverse reactions reported for Fluarix Tetra are listed per dose according to the following frequency categories: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000).

Clinical trial data

Adults

A study with Fluarix Tetra in adults has evaluated the incidence of adverse reactions in subjects ≥18 years who received one dose of Fluarix Tetra (N = 3,036) or Fluarix (N = 1,010).

The following adverse reactions per dose have been reported:

Adverse Reactions	Frequency
Myalgia, injection site pain, fatigue	Very common
Headache, gastrointestinal symptoms (including nausea, vomiting, diarrhoea and/or abdominal pain), sweating[1], arthralgia, injection site redness, injection site swelling, shivering, fever, injection site induration[1]	Common
Dizziness[2], injection site hematoma[2], injection site pruritus[2]	Uncommon

[1]Reported in previous Fluarix trials
[2]Reported as unsolicited adverse reaction

Children aged 6 months to <18 years

Two clinical studies evaluated the reactogenicity and safety of Fluarix Tetra in children who received at least one dose of Fluarix Tetra or a control vaccine.

One study enrolled children 3 to <18 years of age who received Fluarix Tetra (N = 915) or Fluarix (N = 912). The second study enrolled children 6 to <36 months of age who received Fluarix Tetra (N = 6,006) or a non-influenza vaccine control (N = 6,012) (see *Pharmacodynamics*).

The following adverse reactions per dose have been reported:

Adverse reactions	Frequency		
	6 to <36 months	3 to <6 years	6 to <18 years
Loss of appetite	Very common	Common	N/A
Irritability/Fussiness	Very common	Very common	N/A
Drowsiness	Very common	Common	N/A
Headache	N/A	N/A	Common
Gastrointestinal symptoms (including nausea, diarrhoea, vomiting and/or abdominal pain)	N/A	N/A	Common
Rash[1]	N/R	Uncommon	Uncommon
Myalgia	N/A	N/A	Very common
Arthralgia	N/A	N/A	Common
Fever (≥38.0 °C)	Common	Common	Common
Fatigue	N/A	N/A	Very common
Injection site pain	Very common	Very common	Very common
Injection site redness	Very common	Very common	Very common
Injection site swelling	Common	Very common	Very common
Shivering	N/A	N/A	Common

Injection site pruritus[1]	N/R	Uncommon	Uncommon
Injection site induration[2]	N/A	Common	Common

N/A=Not solicited in this age group
N/R=Not reported
[1]Reported as unsolicited adverse reaction
[2]Reported in previous Fluarix trials

Post-marketing data

The following adverse events have been observed for Fluarix and/or Fluarix Tetra during post-marketing surveillance[1].

Adverse reactions	Frequency
Transient lymphadenopathy, allergic reactions (including anaphylactic reactions), neuritis, acute disseminated encephalomyelitis, Guillain-Barré syndrome (GBS)[2], urticaria, pruritus, erythema, angioedema, influenza-like illness, malaise	Rare

[1]Three of the influenza strains contained in Fluarix are included in Fluarix Tetra.
[2]Spontaneous reports of GBS have been received following vaccination with Fluarix and Fluarix Tetra; however, a causal association between vaccination and GBS has not been established.

4. PHARMACOLOGICAL PROPERTIES

4.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccine, ATC Code: J07BB02

Mechanism of action

Fluarix Tetra induces haemagglutination-inhibition (HI) antibodies against the 4 influenza virus strains contained in the vaccine. While specific levels of HI antibody in response to inactivated influenza virus vaccines have not been correlated with protection from influenza illness, the HI antibody titres have been used as a measure of vaccine activity. In some human challenge studies, HI antibody titres of ≥1:40 have been associated with protection from influenza illness in up to 50% of subjects.

Pharmacodynamic effects

Efficacy in children 6-35 months of age

The vaccine efficacy (VE) of Fluarix Tetra was evaluated in study D-QIV-004, a randomised, observer-blind, non-influenza vaccine-controlled trial conducted during influenza seasons 2011 to 2014. Healthy subjects aged 6 through 35 months were randomized (1:1) to receive Fluarix Tetra (N = 6,006) or an age appropriate non-influenza control vaccine (N = 6,012). Subjects were administered 1 dose (in case of history of influenza vaccination) or 2 doses, approximately 28 days apart.

VE of Fluarix Tetra was assessed for the prevention of influenza A and/or B disease (moderate to severe and of any severity) due to any seasonal influenza strain, starting 2 weeks post-vaccination until the end of the influenza season (approximately 6 months later). Fluarix Tetra met the predefined criteria for primary and secondary VE objectives (Table 1).

Table 1: Attack rates and VE in children 6-35 months of age (ATP (according to protocol) cohort for efficacy – time to event).

	Fluarix Tetra (N = 5,707)	Active comparator (N = 5,697)	Vaccine Efficacy	
	Attack rate (%)	Attack rate (%)	%	CI
Any severity Influenza[1]				
RT-PCR[3] confirmed	6.03	11.62	49.8	41.8; 56.8[4]
Culture confirmed	5.31	10.57	51.2	44.1; 57.6[5]
Culture confirmed vaccine matching strains	1.54	3.79	60.1	49.1; 69.0[5]
Moderate to Severe Influenza[2]				
RT-PCR[3] confirmed	1.58	4.25	63.2	51.8; 72.3[4]
Culture confirmed	1.38	3.79	63.8	53.4; 72.2[5]
Culture confirmed vaccine matching strains	0.35	1.54	77.6	64.3; 86.6[5]
Lower respiratory illness RT-PCR[3] confirmed	0.49	1.07	54.0	28.9; 71.0[5]
Acute otitis media RT-PCR[3] confirmed	0.21	0.49	56.6	16.7; 78.8[5]

[1]Defined as an episode of influenza-like illness (ILI, i.e. fever ≥38 °C with any of the following: cough, runny nose, nasal congestion, or breathing difficulty) or a consequence of influenza virus injection [acute otitis media (AOM) or lower respiratory illness (LRI)]
[2]Defined as a subset of any influenza disease, with any of the following: fever >39 °C, physician-diagnosed AOM, physician-diagnosed lower respiratory tract infection, physician-diagnosed serious extra-pulmonary complication, hospitalisation in the intensive care unit, or supplemental oxygen required for more than 8 hours.
[3]reverse transcription polymerase chain reaction
[4]2-sided 97.5% confidence interval
[5]2-sided 95% confidence interval

Exploratory analyses were conducted on the Total Vaccinated Cohort (TVC) including 12,018 subjects. Fluarix Tetra was efficacious in the prevention of moderate to severe influenza caused by each of the 4 strains (Table 2), even when there was significant antigenic mismatch with 2 of the vaccine strains (A/H3N2 and B/Victoria).

Table 2: Attack rates and VE for RT-PCR confirmed moderate to severe disease by Influenza A subtypes and Influenza B lineages in children 6-35 months of age (TVC).

Strain	Fluarix Tetra (N = 6,006)	Active comparator (N =6,012)	Vaccine Efficacy	
	Attack rate (%)	Attack rate (%)	%	95% CI
A/H1N1[1]	0.22	0.77	72.1	49.9; 85.5
A/H3N2[2]	0.88	1.86	52.7	34.8; 66.1
B/Victoria[3]	0.05	0.25	80.1	39.7; 95.4
B/Yamagata[4]	0.37	1.21	70.1	52.7; 81.9

[1 to 4]Proportion of antigenic matching strains was 84.8%, 2.6%, 14.3% and 66.6%, for A/H1N1, A/H3N2, B/Victoria, and B/Yamagata, respectively.

Additionally, for RT-PCR confirmed cases of severity, Fluarix Tetra reduced the risk of visits to the general practitioner by 47% (Relative Risk (RR): 0.53 [95% CI: 0.46; 0.61], i.e., 310 versus 583 visits) and to the emergency room by 79% (RR: 0.21 [95% CI: 0.09; 0.47], i.e., 7 versus 33 visits). The use of antibiotics was reduced by 50% (RR: 0.50 [95% CI: 0.42; 0.60], i.e., 172 versus 341 subjects).

Immunogenicity in children and adults

Immunogenicity of Fluarix Tetra was evaluated in terms of HI geometric mean antibody titre (GMT) at 28 days after the last dose (children) or Day 21 (adults) and HI seroconversion rate (4-fold rise in reciprocal titre or change from undetectable [<10] to a reciprocal titre of ≥40).

In study D-QIV-004, the evaluation was performed in a sub-cohort of 1,332 children (Table 3).

The effect of a 2-dose priming schedule in D-QIV-004 was evaluated by assessing the immune response after revaccination one year later with 1 dose of Fluarix Tetra in study D-QIV-009. This study demonstrated that 7 days post-vaccination, immune memory in children 6 to 35 months of age had been elicited for all 4 vaccine strains.

Immunogenic non-inferiority of Fluarix Tetra was assessed versus Fluarix in children (study D-QIV-003) and in adults (study D-QIV-008). Children received 1 or 2 doses and adults received 1 dose of either vaccine. In both studies, Fluarix Tetra elicited an immune response against the 3 strains in common that was non-inferior to Fluarix and a superior immune response against the additional B strain included in Fluarix Tetra (Table 3).

Table 3: Post-vaccination GMT and seroconversion rates (SCR) in children [6-35 months; 3 to <18 years; and adults ≥ 18 years (ATP (95% CI))].

Children 6 to 35 months of age (D-QIV-004)				
	Fluarix Tetra		**Control**	
	N=750-753	**N'=742-746**	**N=578-579**	**N'=566-568**
	GMT[1]	**SCR[1]**	**GMT[1]**	**SCR[1]**
A/H1N1	165.3 (148.6; 183.8)	80.2% (77.2; 83.0)	12.6 (11.1; 14.3)	3.5% (2.2; 5.4)
A/H3N2	132.1 (119.1; 146.5)	68.8% (65.3; 72.1)	14.7 (12.9; 16.7)	4.2% (2.7; 6.2)
B (Victoria)	92.6 (82.3; 104.1)	69.3% (65.8; 72.6)	9.2 (8.4; 10.1)	0.9% (0.3; 2.0)
B (Yamagata)	121.4 (110.1; 133.8)	81.2% (78.2; 84.0)	7.6 (7.0; 8.3)	2.3% (1.2; 3.9)
Children 3 to <18 years (D-QIV-003)				
	Fluarix Tetra		**Fluarix[2]**	
	N=791	**N'=790**	**N=818**	**N'=818**
	GMT	**SCR**	**GMT**	**SCR**
A/H1N1	386.2 (357.3; 417.4)	91.4% (89.2; 93.3)	433.2 (401.0; 468.0)	89.9% (87.6; 91.8)
A/H3N2	228.8 (215.0; 243.4)	72.3% (69.0; 75.4)	227.3 (213.3; 242.3)	70.7% (67.4; 73.8)
B (Victoria)	244.2 (227.5; 262.1)	70.0% (66.7; 73.2)	245.6 (229.2; 263.2)	68.5% (65.2; 71.6)
B (Yamagata)	569.6 (533.6; 608.1)	72.5% (69.3; 75.6)	224.7 (207.9; 242.9)	37.0% (33.7; 40.5)

Adults ≥ 18 years (D-QIV-008)				
	Fluarix Tetra		**Fluarix[2]**	
	N=1,809	**N'=1,801**	**N=608**	**N'=605**
	GMT	**SCR**	**GMT**	**SCR**
A/H1N1	201.1 (188.1; 215.1)	77.5% (75.5; 79.4)	218.4 (194.2; 245.6)	77.2% (73.6; 80.5)
A/H3N2	314.7 (296.8; 333.6)	71.5% (69.3; 73.5)	298.2 (268.4; 331.3)	65.8% (61.9; 69.6)
B (Victoria)	404.6 (386.6; 423.4)	58.1% (55.8; 60.4)	393.8 (362.7; 427.6)	55.4% (51.3; 59.4)
B (Yamagata)	601.8 (573.3; 631.6)	61.7% (59.5; 64.0)	386.6 (351.5; 425.3)	45.6% (41.6; 49.7)

N = Number of subjects with post-vaccination results available (for GMT)
N' = Number of subjects with both pre- and post-vaccination results available (for SCR)
[1]Results from the immunogenicity sub-cohort
[2]B (Yamagata) strain was not included in Fluarix

Concomitant administration with pneumococcal vaccines

In clinical study D-QIV-010 involving 356 adults ≥ 50 years of age at risk for complications of influenza and pneumococcal diseases, subjects received Fluarix Tetra and 23-valent pneumococcal polysaccharide vaccine (PPV23) either concomitantly or separately. For all 4 Fluarix Tetra vaccine strains and the 6 pneumococcal serotypes (1, 3, 4, 7F, 14, and 19A) in PPV23 evaluated in the pre-specified primary analysis, the immune response was non-inferior between the 2 treatment groups. Based on a descriptive analysis for 6 additional pneumococcal vaccine serotypes (5, 6B, 9V, 18C, 19F and 23F), the immune response was comparable between groups, with 91.7% to 100% and 90.7% to 100% of subjects attaining seroprotective antibody levels against these serotypes in the separate and concomitant administration group respectively.

Concomitant administration with adjuvanted herpes zoster vaccine (Shingrix)

In clinical study Zoster-004, 828 adults ≥ 50 years of age were randomized to receive 2 doses of Shingrix 2 months apart, administered either concomitantly at the first dose (N=413) or non-concomitantly (N=415) with one dose of Fluarix Tetra. The antibody responses to each vaccine were similar, whether administered concomitantly or non-concomitantly. Furthermore, immunological non-inferiority between concomitant and non-concomitant administration was demonstrated for all four strains included in Fluarix Tetra in terms of HI antibody GMTs.

4.2 Non-Clinical Information

Non-clinical data revealed no special hazards to humans based on conventional studies of acute toxicity, local tolerance, repeated dose toxicity and reproductive/developmental toxicity.

5. PHARMACEUTICAL INFORMATION

5.1 List of excipients

Sodium chloride, disodium phosphate dodecahydrate, potassium dihydrogen phosphate, potassium chloride, magnesium chloride hexahydrate, α-tocopheryl hydrogen succinate, polysorbate 80, octoxinol 10 and water for injection.

Hydrocortisone, gentamicin sulphate, ovalbumin, formaldehyde and sodium deoxycholate are present as residue from the manufacturing process.

5.2 Shelf life

The expiry date is indicated on the label and packaging.

5.3 Storage

Store at 2 °C – 8 °C (in a refrigerator).

Do not freeze.

Store in the original package in order to protect from light. The storage conditions are detailed on the packaging.

5.4 Nature and contents of the container

0.5 ml suspension in prefilled syringe (Type I glass) with a plunger stopper (grey butyl rubber) with fixed or separate or without needles in the following pack sizes:

- with fixed needle: pack sizes of 1 or 10
- with 1 separate needle: pack sizes of 1 or 10
- with 2 separate needles: pack size of 1
- without needle: pack sizes of 1 or 10

The needle type(s) that may be supplied in the pack are: 23G 1", 25G 5/8" and 25G 1".

5.5 Incompatibilities

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

5.6 Special precautions for disposal and other handling

The vaccine should be allowed to reach room temperature before use.

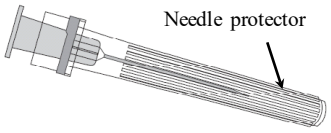
The vaccine presents as a colourless to slightly opalescent suspension.

The syringe should be shaken and inspected visually for any foreign particulate matter and/or variation of physical aspect prior to administration. In the event of either being observed, discard the vaccine.

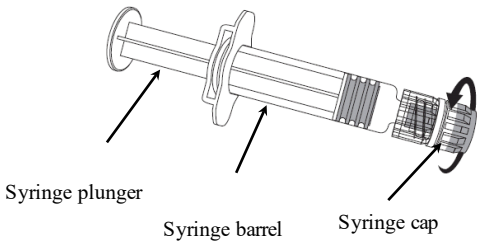
<u>Instructions for administration of the vaccine presented in pre-filled syringe without a fixed needle</u>

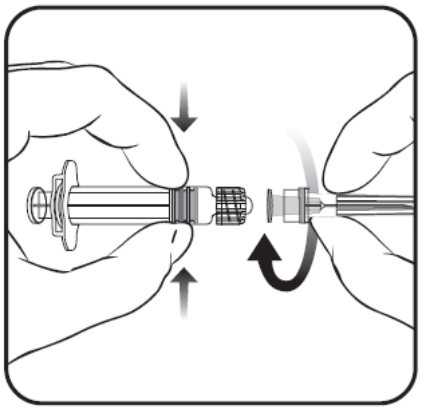
To attach the needle to the syringe, refer to the below drawing. However, the syringe provided with Fluarix Tetra might be slightly different (without screw thread) than the syringe described in the drawing. In that case, the needle should be attached without screwing.

Needle



Syringe





1. Holding the syringe **barrel** in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.
2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock. (See picture)
3. Remove the needle protector, which on occasion can be a little stiff.
4. Administer the vaccine.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Not all presentations are available in every country.

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