Quadrivalent Seasonal Influenza Vaccine (Split Virion, Inactivated) Southern Hemisphere 2023

Fluarix Tetra SH2023
Vaccine

QUALITATIVE AND QUANTITATIVE COMPOSITION

Quadrivalent Seasonal Influenza Vaccine (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).

This vaccine complies with the WHO recommended strains (Southern Hemisphere) for the season 2023.

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

Quadrivalent Seasonal Influenza Vaccine (Fluarix Tetra) meets the WHO requirements for biological substances and influenza vaccines and the European Pharmacopoeia requirements for influenza vaccines.

PHARMACEUTICAL FORM

Suspension for injection.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Mechanism of Action

Quadrivalent Seasonal Influenza Vaccine (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.

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

Pharmacodynamic Effects

Efficacy in children 6-35 months of age:

The vaccine efficacy (VE) of Quadrivalent Seasonal Influenza Vaccine (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 randomised (1:1) to receive Quadrivalent Seasonal Influenza Vaccine (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 Quadrivalent Seasonal Influenza Vaccine (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). Quadrivalent Seasonal Influenza Vaccine (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)

	Quadrivalent Seasonal Influenza Vaccine (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 Confirmed	0.49	1.07	54.0	28.9; 71.0[5]
Acute Otitis media RT PCR-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 infection [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 complications, 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. Quadrivalent Seasonal Influenza Vaccine (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	Quadrivalent Seasonal Influenza Vaccine (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 any severity, Quadrivalent Seasonal Influenza Vaccine (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 Quadrivalent Seasonal Influenza Vaccine (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 Quadrivalent Seasonal Influenza Vaccine (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 Quadrivalent Seasonal Influenza Vaccine (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, Quadrivalent Seasonal Influenza Vaccine (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 Quadrivalent Seasonal Influenza Vaccine (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 Quadrivalent Seasonal Influenza Vaccine (Fluarix Tetra) and 23-valent pneumococcal polysaccharide vaccine (PPV23) either concomitantly or separately. For all 4 Quadrivalent Seasonal Influenza Vaccine (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 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.

Immunological non-inferiority has been demonstrated based on published data for all 3 Fluarix trivalent strains (D-TIV) and all 13-valent pneumococcal conjugate vaccine (PCV13) serotypes in adults 50-59 years of age, as well as for 2 of 3 D-TIV strains and 12 of 13 PCV13 serotypes in adults >65 years of age. A lower immune response to some pneumococcal serotypes was observed when PCV13 was given concomitantly with D-TIV as compared to separate administration, however the clinical relevance of this observation is unknown.

Non-Clinical Information

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

CLINICAL INFORMATION

Indications

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

The use of Quadrivalent Seasonal Influenza Vaccine (Fluarix Tetra) should be based on official recommendations.

Dosage and Administration

Quadrivalent Seasonal Influenza Vaccine (Fluarix Tetra) should be administered as a single 0.5 ml injection.

Children 6 months to less than 9 years of age 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 Quadrivalent Seasonal Influenza Vaccine (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).

Contraindications

Quadrivalent Seasonal Influenza Vaccine (Fluarix Tetra) should not be administered to subjects with known hypersensitivity after previous administration of Quadrivalent Seasonal Influenza Vaccine (Fluarix Tetra) or influenza vaccines or to any component of the vaccine.

Warnings and Precautions

It is good clinical practice to precede vaccination by a review of the medical history (especially with regard 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.

As with other vaccines, vaccination with Quadrivalent Seasonal Influenza Vaccine (Fluarix Tetra) should be postponed in subjects suffering from an acute severe febrile illness. The presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

It may be expected that in patients receiving immunosuppressive treatment or patients with immunodeficiency, an adequate immune response may not be elicited.

Quadrivalent Seasonal Influenza Vaccine (Fluarix Tetra) is not effective against all possible strains of influenza virus. Quadrivalent Seasonal Influenza Vaccine (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.

QUADRIVALENT SEASONAL INFLUENZA VACCINE (Fluarix Tetra) SHOULD UNDER NO CIRCUMSTANCES BE ADMINISTERED INTRAVASCULARLY.

As with other vaccines administered intramuscularly, Quadrivalent Seasonal Influenza Vaccine (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 as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

Interactions

Quadrivalent Seasonal Influenza Vaccine (Fluarix Tetra) can be concomitantly administered with pneumococcal vaccines (see *Pharmacodynamics*).

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

False positive ELISA serologic tests for HIV-1, Hepatitis C, and especially HTLV-1 may occur following influenza vaccination. These transient false-positive results may be due to cross-reactive IgM elicited by the vaccine. For this reason, a definitive diagnosis of HIV-1, Hepatitis C, or HTLV-1 infection requires a positive result from a virus-specific confirmatory test (e.g. Western Blot or immunoblot).

Pregnancy and Lactation

The vaccine may be administered to pregnant women following an assessment of the risks and benefits.

The safety of Quadrivalent Seasonal Influenza Vaccine (Fluarix Tetra) when administered to pregnant women has not been evaluated in clinical trials.

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

Animal studies with Quadrivalent Seasonal Influenza Vaccine (Fluarix Tetra) do not indicate direct or indirect harmful effects with respect to reproductive and developmental toxicity (see *Non-clinical Information*).

The safety of Quadrivalent Seasonal Influenza Vaccine (Fluarix Tetra) when administered to breast-feeding women has not been evaluated. It is unknown whether Quadrivalent Seasonal Influenza Vaccine (Fluarix Tetra) is excreted in human breast milk.

Quadrivalent Seasonal Influenza Vaccine (Fluarix Tetra) should only be used during breast-feeding when the possible advantages outweigh the potential risks.

Adverse Reactions

Adverse reactions reported for Quadrivalent Seasonal Influenza Vaccine (Fluarix Tetra) 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); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000).

Clinical trial data

Adults

A study with Quadrivalent Seasonal Influenza Vaccine (Fluarix Tetra) in adults has evaluated the incidence of adverse reactions in subjects ≥18 years who received one dose of Quadrivalent Seasonal Influenza Vaccine (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 Quadrivalent Seasonal Influenza Vaccine (Fluarix Tetra) in children who received at least one dose of Quadrivalent Seasonal Influenza Vaccine (Fluarix Tetra) or a control vaccine.

One study enrolled children 3 to <18 years of age who received Quadrivalent Seasonal Influenza Vaccine (Fluarix Tetra) (N = 915) or Fluarix (N = 912). The second study enrolled children 6 to <36 months of age who received Quadrivalent Seasonal Influenza Vaccine (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 reactions have been observed for Fluarix and/or Quadrivalent Seasonal Influenza Vaccine (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 Quadrivalent Seasonal Influenza Vaccine (Fluarix Tetra).
[2]Spontaneous reports of GBS have been received following vaccination with Fluarix and Quadrivalent Seasonal Influenza Vaccine (Fluarix Tetra); however, a causal association between vaccination and GBS has not been established.

PHARMACEUTICAL INFORMATION

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 injections.

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

Shelf Life

The expiry date is indicated on the label and packaging.

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.

Nature and Contents of Container

0.5 ml in pre-filled syringe (type I glass) – pack size of 1's.

Incompatibilities

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

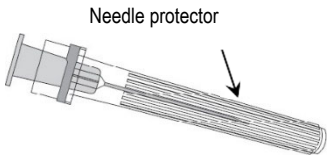
Use and Handling

The vaccine presents as a colourless to slightly opalescent suspension.

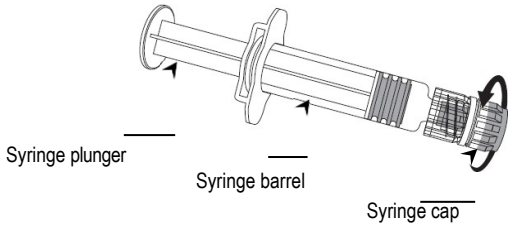
The syringe should be shaken and inspected visually for any foreign particulate matter and/or variation of physical aspect prior to administration. In the event of either being observed, discard the vaccine.

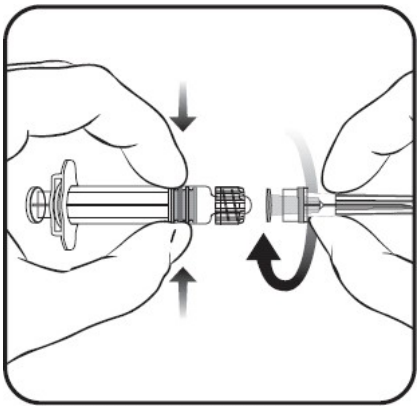
Instructions for administration of the vaccine presented in a PRTC pre-filled syringe

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

Not all presentations are available in every country.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription. Keep all medicines out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
Seek medical attention immediately at the first sign of any adverse drug reaction.

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