

FLUARIX™ TETRA
PRODUCT INFORMATION

NAME OF THE MEDICINE

Quadrivalent influenza vaccine (split virion, inactivated)

DESCRIPTION

Fluarix Tetra is an inactivated and purified split influenza vaccine. The antigen composition and strains for the 2013 influenza season corresponds to the following types:

A/California/7/2009-like virus

A/Victoria/361/2011-like virus

B/Wisconsin/1/2010-like virus

B/Brisbane/60/2008-like virus

Fluarix Tetra is prepared using whole virus cultivated in embryonated hens' eggs. The virus is concentrated and purified by clarification, adsorption and centrifugation. The purified whole virus is then treated with the detergent sodium deoxycholate and again centrifuged, and the resulting antigen suspension is inactivated with formaldehyde.

Suspension for injection.

Fluarix Tetra is a colourless to slightly opalescent suspension.

Each 0.5 ml vaccine dose contains 15 µg haemagglutinin of each of four influenza strains in phosphate buffered saline. The vaccine preparation also contains polysorbate 80, octoxinol 10, α-tocopheryl hydrogen succinate, sodium chloride, disodium phosphate dodecahydrate, potassium dihydrogen phosphate, potassium chloride, magnesium chloride hexahydrate, water for injections.

May contain residual amounts of the following process related impurities: hydrocortisone, gentamicin sulfate, ovalbumin, formaldehyde, and sodium deoxycholate.

The manufacture of this product includes exposure to bovine derived materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

Attachment 1: Product information for AusPAR Fluarix Tetra Influenza virus haemagglutinin inactivated split influenza vaccine GlaxoSmithKline Australia Pty Ltd PM-2012-02287-3-2 Final 6 February 2014. This Product Information was approved at the time this AusPAR was published.

Fluarix Tetra meets the WHO requirements for biological substances and influenza vaccines and the European Pharmacopoeia requirements for influenza vaccines.

The type and amount of viral antigens in Fluarix Tetra conform to the annual requirements of the Australian Influenza Vaccine Committee (AIVC) and the New Zealand Ministry of Health.

PHARMACOLOGY

Pharmacotherapeutic group: Influenza vaccines, ATC Code J07BB02.

Fluarix Tetra provides active immunisation against the four influenza virus strains (two A subtypes and two B strains) contained in the vaccine. Fluarix Tetra induces humoral antibodies against the haemagglutinins. These antibodies neutralise influenza viruses. Specific levels of haemagglutination-inhibition (HI) antibody titer post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza illness but the HI antibody titers have been used as a measure of vaccine activity. In some human challenge studies, HI antibody titres of $\geq 1:40$ have been associated with protection from influenza illness in up to 50% of individuals.

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. Protection afforded as a result of vaccination with Fluarix Tetra is specific to the influenza strains contained in Fluarix Tetra or to closely related strains.

CLINICAL TRIALS

Clinical studies performed in adults (D-QIV-001 and D-QIV-008) and in children 3 years to 17 years of age (D-QIV-003) assessed the non-inferiority of the antigen components common to Fluarix Tetra versus trivalent influenza vaccines (TIV) - Fluarix[®] (TIV-1) and TIV-2 (an alternate trivalent formulation containing the same A strains as TIV-1 but the B strain of the other lineage present in D-QIV), and the immunological superiority for the additional B strain unique to Fluarix Tetra. HI antibody Geometric Mean Titer (GMT) at Day 21 (for adults) and at 28 days after the final vaccination (for children) and HI seroconversion rate (Seroconversion rate was defined as the percentage of individuals who had either a pre-vaccination titre $< 1:10$ and a post-vaccination titre $\geq 1:40$ or pre-

Attachment 1: Product information for AusPAR Fluarix Tetra Influenza virus haemagglutinin inactivated split influenza vaccine GlaxoSmithKline Australia Pty Ltd PM-2012-02287-3-2 Final 6 February 2014. This Product Information was approved at the time this AusPAR was published.

vaccination titre \geq 1:10 and at least a 4-fold increase in post-vaccination titre) were evaluated for each antigen.

In all comparative studies, the immune response elicited by Fluarix Tetra against the three strains common to both vaccines was non-inferior. Fluarix Tetra elicited a superior immune response against the unique B strain not included in the comparator TIV (Fluarix or TIV-2).

Adults 18 years of age and older

In clinical study D-QIV-008, the evaluable population was approximately 1,800 adults 18 years of age and older who received a single dose of Fluarix Tetra, approximately 600 individuals who received a single dose of TIV-1 (Fluarix), and approximately 530 individuals who received a single dose of TIV-2.

Table 1: Post-vaccination GMT and seroconversion rates in clinical study D-QIV-008:

Adults 18 years of age and older	Fluarix Tetra ¹ N=1809	TIV-1 (Fluarix) ² N=608	TIV-2 ³ N=534
GMT (95% confidence interval)			
A/H1N1	201.1 (188.1;215.1)	218.4 (194.2;245.6)	213.0 (187.6;241.9)
A/H3N2	314.7 (296.8;333.6)	298.2 (268.4;331.3)	340.4 (304.3;380.9)
B (Victoria)	404.6 (386.6;423.4)	393.8 (362.7;427.6)	258.5 (234.6;284.8) ⁴
B (Yamagata)	601.8 (573.3;631.6)	386.6 (351.5;425.3) ⁴	582.5 (534.6;634.7)
Seroconversion rate (95% confidence interval)			
A/H1N1	77.5% (75.5;79.4)	77.2% (73.6;80.5)	80.2% (76.5;83.5)
A/H3N2	71.5% (69.3;73.5)	65.8% (61.9;69.6)	70.0% (65.9;73.9)
B (Victoria)	58.1% (55.8;60.4)	55.4% (51.3;59.4)	47.5% (43.2;51.9) ⁴
B (Yamagata)	61.7% (59.5;64.0)	45.6% (41.6;49.7) ⁴	59.1% (54.7;63.3)

¹containing A/H1N1, A/H3N2 and B (Victoria lineage) and B (Yamagata lineage). The two A subtypes plus the B (Victoria) strain constitute the TIV vaccine as recommended by WHO for the Northern Hemisphere season 2010-2011. The B (Yamagata) was recommended by WHO for the Northern Hemisphere season 2008-2009.

²containing A/H1N1, A/H3N2 and B (Victoria lineage)

³containing A/H1N1, A/H3N2 and B (Yamagata lineage)

⁴B strain not included in comparator TIV vaccine. Immunological responses to the B strain not contained in the TIV are indicative of the non-naive status of most individuals from prior vaccination or exposure to circulating strains.

Post-vaccination seroprotection rates (Day 21 reciprocal titer of \geq 40) for Fluarix Tetra were 91.3% against A/H1N1, 96.8% against A/H3N2, 98.8% against B (Victoria) and 99.1% against B (Yamagata).

Attachment 1: Product information for AusPAR Fluarix Tetra Influenza virus haemagglutinin inactivated split influenza vaccine GlaxoSmithKline Australia Pty Ltd PM-2012-02287-3-2 Final 6 February 2014. This Product Information was approved at the time this AusPAR was published.

In clinical study D-QIV-001 (vaccine composition of 2007-2008 season), post-vaccination seroprotection rates for Fluarix Tetra were 92.3% against A/H1N1, 97.1% against A/H3N2, 97.1% against B (Victoria) and 98.1% against B (Yamagata). Seroprotection was defined as the percentage of individuals with a serum HI titre \geq 1:40.

Children 3-17 years of age

In clinical study (D-QIV-003), the evaluable population was approximately 800 children from 3-17 years of age who received Fluarix Tetra or TIV-1 (Fluarix), and approximately 500 children who received TIV-2; one dose for primed individuals or two doses for naive individuals.

Table 2: Post-vaccination GMT and seroconversion rates in clinical study D-QIV-003

Children 3 years to 17 years of age	Fluarix Tetra¹ N=791	TIV-1 (Fluarix)² N=818	TIV-2³ N=534
	GMT (95% confidence interval)		
A/H1N1	386.2 (357.3;417.4)	433.2 (401.0;468.0)	422.3 (390.5;456.5)
A/H3N2	228.8 (215.0;243.4)	227.3 (213.3;242.3)	234.0 (219.1;249.9)
B (Victoria)	244.2 (227.5;262.1)	245.6 (229.2;263.2)	88.4 (81.5;95.8) ⁴
B (Yamagata)	569.6 (533.6;608.1)	224.7 (207.9;242.9) ⁴	643.3 (603.2;686.1)
	Seroconversion rate (95% confidence interval)		
A/H1N1	91.4% (89.2;93.3)	89.9% (87.6;91.8)	91.6 (89.5;93.5)
A/H3N2	72.3% (69.0;75.4)	70.7% (67.4;73.8)	71.9 (68.6;75.0)
B (Victoria)	70.0% (66.7;73.2)	68.5% (65.2;71.6)	29.6 (26.5;32.9) ⁴
B (Yamagata)	72.5% (69.3;75.6)	37.0% (33.7;40.5) ⁴	70.8 (67.5;73.9)

¹containing A/H1N1, A/H3N2 and B (Victoria lineage) and B (Yamagata lineage). The two A subtypes plus the B (Victoria lineage) constitute the TIV vaccine as recommended by WHO for the Northern Hemisphere season 2010-2011. The B (Yamagata) was recommended by WHO for the Northern Hemisphere season 2008-2009.

²containing A/H1N1, A/H3N2 and B (Victoria lineage)

³containing A/H1N1, A/H3N2 and B (Yamagata lineage)

⁴B strain not included in comparator TIV vaccine. Immunological responses to B strains not contained in the TIV are indicative of primed individuals following prior vaccination or exposure to circulating strains.

Post-vaccination seroprotection rates for Fluarix Tetra were 96.6% against A/H1N1, 98.0% against A/H3N2, 97.3% against B (Victoria) and 99.2% against B (Yamagata).

INDICATIONS

Fluarix Tetra is a quadrivalent vaccine indicated for active immunisation of adults and children from 3 years of age for the prevention of influenza disease caused by the influenza virus types A and B contained in the vaccine.

Attachment 1: Product information for AusPAR Fluarix Tetra Influenza virus haemagglutinin inactivated split influenza vaccine GlaxoSmithKline Australia Pty Ltd PM-2012-02287-3-2 Final 6 February 2014. This Product Information was approved at the time this AusPAR was published.

The use of Fluarix Tetra should be based on official recommendations

CONTRAINDICATIONS

Fluarix Tetra should not be administered to individuals with known hypersensitivity after previous administration of Fluarix Tetra or influenza vaccines or to any component of the vaccine.

PRECAUTIONS

Fluarix Tetra should under no circumstances be administered intravascularly.

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 Fluarix Tetra should be postponed in individuals 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.

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.

Patients with a history of Guillain-Barre Syndrome (GBS) with an onset within six weeks of an influenza vaccination may be at increased risk of again developing GBS if given influenza vaccine. Such risk should be weighed against the benefits to the individual patient of influenza vaccination.

As patients with a history of GBS have an increased likelihood of again developing the syndrome, the chance of them coincidentally developing the syndrome following influenza vaccination may be higher than in individuals with no history of GBS.

Attachment 1: Product information for AusPAR Fluarix Tetra Influenza virus haemagglutinin inactivated split influenza vaccine GlaxoSmithKline Australia Pty Ltd PM-2012-02287-3-2 Final 6 February 2014. This Product Information was approved at the time this AusPAR was published.

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

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 individuals.

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.

Effects on fertility:

A reproductive and developmental toxicity study in which female rats were administered Fluarix Tetra (0.2 mL dose per rat, approximately 80x the human dose on the basis of bodyweight) twice prior to mating showed no adverse effects on female fertility.

Use in Pregnancy (Category B1):

The safety of Fluarix Tetra when administered to pregnant women has not been evaluated. A reproductive and developmental toxicity study in which female rats were administered Fluarix Tetra by IM injection (0.2 mL dose per rat, approximately 80x the human dose on the basis of bodyweight) twice prior to mating, four times during gestation, and once on lactation day 7, showed no adverse effects on female fertility, pregnancy, parturition, lactation, and embryofoetal and pre-weaning development. Vaccine antigen-specific antibodies were detected in foetuses and pups of treated rats.

Fluarix Tetra should be used during pregnancy only when clearly needed, and when the possible advantages outweigh the potential risks for the mother or foetus.

Use in Lactation:

The safety of Fluarix Tetra when administered to breastfeeding women has not been evaluated. It is unknown whether Fluarix Tetra is excreted in human breast milk.

Vaccine antigen-specific antibodies were transferred to rat pups via milk from dams administered Fluarix Tetra during gestation and lactation, with no adverse effects.

Fluarix Tetra should only be used during breast-feeding when the possible advantages outweigh the potential risks.

Attachment 1: Product information for AusPAR Fluarix Tetra Influenza virus haemagglutinin inactivated split influenza vaccine GlaxoSmithKline Australia Pty Ltd PM-2012-02287-3-2 Final 6 February 2014. This Product Information was approved at the time this AusPAR was published.

Genotoxicity:

Fluarix Tetra has not been tested for genotoxic potential.

Carcinogenicity:

Fluarix Tetra has not been tested for carcinogenic potential.

Use in geriatrics:

Antibody responses were lower in geriatric subjects who received Fluarix Tetra than in younger subjects. In a randomized, double-blind (2 arms) and open-label (one arm), active-controlled study, immunogenicity and safety were evaluated in a cohort of subjects 65 years of age and older who received Fluarix Tetra (N = 1,517); 469 of these subjects were 75 years of age and older. In subjects 65 years of age and older, the geometric mean antibody titers post-vaccination and seroconversion rates were lower than in younger subjects (18 through 64 years of age) and the frequencies of solicited and unsolicited adverse events were generally lower than in younger subjects.

Effect on Laboratory Tests:

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).

Latex:

The removable rubber needle shield of the prefilled syringes contains natural rubber latex, and therefore Fluarix-Tetra cannot be considered latex-free.

INTERACTIONS WITH OTHER MEDICINES

No interaction studies have been performed. 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.

Influenza vaccine can impair the metabolism of warfarin, theophylline, phenytoin, phenobarbitone and carbamazepine by the hepatic cytochrome P450 system. Results from studies have been variable in degree of interaction and time after vaccination for the interaction to take effect. The interaction may be variable from individual to individual. Patients taking warfarin, theophylline, phenytoin, phenobarbitone or carbamazepine

Attachment 1: Product information for AusPAR Fluarix Tetra Influenza virus haemagglutinin inactivated split influenza vaccine GlaxoSmithKline Australia Pty Ltd PM-2012-02287-3-2 Final 6 February 2014. This Product Information was approved at the time this AusPAR was published.

should be advised of the possibility of an interaction and told to look out for signs of elevated levels of their medication.

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

ADVERSE EFFECTS

Clinical trial data

In two clinical studies, adults 18 years of age and older and children 3 years to 17 years of age were administered Fluarix Tetra (more than 3,000 adults and 900 children) or Fluarix (more than 1,000 adults and 900 children). Similar rates of solicited adverse events were observed in recipients of Fluarix Tetra and Fluarix.

Adverse reactions reported for Fluarix Tetra are listed according to the following frequency categories:

Very common $\geq 1/10$

Common $\geq 1/100$ to $< 1/10$

Uncommon $\geq 1/1,000$ to $< 1/100$

Rare $\geq 1/10,000$ to $< 1/1,000$

Very rare $< 1/10,000$

Adverse events observed in children 3 years to 17 years of age:

Metabolism and nutrition disorders

Common: appetite loss¹

Psychiatric disorders

Very common: irritability¹ Nervous system disorders

Common: drowsiness¹, headache

Gastrointestinal disorders

Common: gastrointestinal symptoms (including nausea, vomiting, diarrhoea and/or abdominal pain)

Skin and subcutaneous tissue disorders

Uncommon: rash

Musculoskeletal and connective tissue disorders

Very common: myalgia

Common: arthralgia

Attachment 1: Product information for AusPAR Fluarix Tetra Influenza virus haemagglutinin inactivated split influenza vaccine GlaxoSmithKline Australia Pty Ltd PM-2012-02287-3-2 Final 6 February 2014. This Product Information was approved at the time this AusPAR was published.

General disorders and administration site conditions

Very common: fatigue, injection site redness, injection site swelling

Common: shivering, fever

Uncommon: injection site pruritis

¹reported as a solicited symptom in individuals less than 6 years of age

Adverse events observed in adults:

Nervous system disorders

Common: headache

Uncommon: dizziness

Gastrointestinal disorders

Common: gastrointestinal symptoms (including nausea, vomiting, diarrhoea and/or abdominal pain)

Skin and subcutaneous tissue disorders

Musculoskeletal and connective tissue disorders

Very common: myalgia

Common: arthralgia

General disorders and administration site conditions

Very common: injection site pain, fatigue

Common: injection site redness¹, injection site swelling¹, shivering, fever

Uncommon: injection site hematoma, injection site pruritus

¹reported in subjects 5 years and older

In addition, the following adverse reactions were reported in previous Fluarix trials:

Skin and subcutaneous tissue disorders

Common: sweating

General disorders and administration site conditions

Common: injection site induration

Post-marketing data

There has been no post-marketing exposure to Fluarix Tetra. The post-marketing experience with Fluarix, which is manufactured according to the same antigen production and formulation process as Fluarix Tetra and is essentially similar other than lacking a second B-strain, identified the following adverse events - these may occur in patients receiving Fluarix Tetra.

Attachment 1: Product information for AusPAR Fluarix Tetra Influenza virus haemagglutinin inactivated split influenza vaccine GlaxoSmithKline Australia Pty Ltd PM-2012-02287-3-2 Final 6 February 2014. This Product Information was approved at the time this AusPAR was published.

Blood and lymphatic system disorders

Rare: transient lymphadenopathy

Immune system disorders

Rare: allergic reactions (including anaphylactic reactions)

Nervous system disorders

Rare: neuritis, acute disseminated encephalomyelitis, Guillain-Barré syndrome*

*Spontaneous reports of Guillain-Barré syndrome have been received following vaccination with Fluarix; however, a causal association between vaccination and Guillain-Barré syndrome has not been established.

Skin and subcutaneous tissue disorders

Rare: urticaria, pruritus, erythema, angioedema

General disorders and administration site conditions

Rare: influenza-like illness, malaise

DOSAGE AND ADMINISTRATION

Fluarix Tetra should under no circumstances be administered intravascularly.

Dosage

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

Children 3 years 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.

Administration

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

Instructions for 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.

Attachment 1: Product information for AusPAR Fluarix Tetra Influenza virus haemagglutinin inactivated split influenza vaccine GlaxoSmithKline Australia Pty Ltd PM-2012-02287-3-2 Final 6 February 2014. This Product Information was approved at the time this AusPAR was published.

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

Fluarix Tetra is for single use in one patient only.

OVERDOSAGE

Insufficient data are available.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Fluarix Tetra is presented in pre-filled syringes as pack sizes of 1 or 10.

The pre-filled syringes are made of neutral glass type I, which conforms to European Pharmacopoeia requirements.

Fluarix Tetra must be stored between +2°C and +8°C and be protected from light.

DO NOT FREEZE. Discard if vaccine has been frozen.

The expiry date of the vaccine is indicated on the label and packaging. The shelf life of Fluarix Tetra is 12 months from the date of manufacture if stored between temperatures of +2°C and +8°C.

Not all pack sizes may be distributed in Australia.

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline Australia Pty Ltd,
Level 4, 436 Johnston Street,
Abbotsford, Victoria, 3067

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

Attachment 1: Product information for AusPAR Fluarix Tetra Influenza virus haemagglutinin inactivated split influenza vaccine GlaxoSmithKline Australia Pty Ltd PM-2012-02287-3-2 Final 6 February 2014. This Product Information was approved at the time this AusPAR was published.

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):
[28 August 2013](#)

Date of most recent amendment: 10 February 2014

[\[FLUARIX™ TETRA\]](#) is a registered trade mark of the GlaxoSmithKline group of companies.

Version 2.0