NAME OF THE MEDICINE
Fluarix inactivated split influenza vaccine suspension for injection

DESCRIPTION
Fluarix is an inactivated and purified split influenza vaccine. The antigen composition and strains for the 2015 influenza season corresponds to the following types:

A/California/7/2009 (H1N1) - like virus
A/Switzerland/9715293/2013 (H3N2) - like virus
B/Phuket/3073/2013 - like virus

Fluarix 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.

Each 0.5 mL vaccine dose contains 15 µg haemagglutinin of each of the recommended strains (total of 45 µg haemagglutinin). The vaccine preparation also contains alpha tocopheryl acid succinate, sodium chloride, magnesium chloride, potassium chloride, potassium phosphate monobasic, sodium phosphate dibasic dodecahydrate, polysorbate 80, and octoxinol 10 in water for injections. Residual amounts of ovalbumin ≤0.05 mcg and formaldehyde ≤5 mcg, but also traces of gentamicin sulfate, hydrocortisone, and sodium deoxycholate from the manufacturing process may be present.

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.

Fluarix 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 conform to the annual requirements of the Australian Influenza Vaccine Committee (AIVC) and the New Zealand Ministry of Health.
PHARMACOLOGY
Fluarix induces humoral antibodies against haemagglutinins, the surface antigens of the virus. These antibodies neutralise influenza viruses and are important in the prevention of infection.

In clinical studies conducted with various formulations of Fluarix during 1992-2001 in adults aged 18-60 years (n=1587), the protection rates (percentage of participants with haemagglutinin inhibition titres >40) ranged from 76-100% (H1N1 strains), 67-100% (H3N2 strains) and 95-100% (B strain). In healthy participants aged > 60 years (n=629), the protection rates against the H1N1, H3N2 and B strains ranged from 72-100%, 69-96% and 92-100% respectively.

Seroprotection is generally obtained within 2 to 3 weeks. The duration of postvaccinal immunity varies but is usually 6-12 months.

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

CLINICAL TRIALS
A clinical study performed in more than 7,600 participants in the Czech Republic and Finland evaluated the efficacy of Fluarix to prevent culture-confirmed influenza A and/or B cases for vaccine antigenically matched strains.

Participants were monitored for influenza-like illnesses followed by culture-confirmed influenza (see below table for results). Influenza-like illness was defined as at least one general symptom (fever ≥37.8°C and/or myalgia) and at least one respiratory symptom (cough and/or sore throat).

Table 1: Attack rates and Vaccine Efficacy against Illness associated with evidence of influenza A or B Infection in adults 18 to 64 years of age (Total Vaccinated Cohort)

<table>
<thead>
<tr>
<th></th>
<th>Attack Rates (n/N)</th>
<th>Vaccine Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
</tr>
<tr>
<td><strong>Antigenically matched, culture-confirmed Influenza</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluarix</td>
<td>5,103</td>
<td>49</td>
</tr>
<tr>
<td>Placebo</td>
<td>2,549</td>
<td>74</td>
</tr>
<tr>
<td><strong>All culture-confirmed Influenza (Matched, Unmatched and Untyped)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluarix</td>
<td>5,103</td>
<td>63</td>
</tr>
<tr>
<td>Placebo</td>
<td>2,549</td>
<td>82</td>
</tr>
</tbody>
</table>

1.  n/N: number of case/total number of participants
2.  CI: Confidence Interval
3.  LL: Lower Limit
4.  There were no vaccine matched culture-confirmed cases of A/New Caledonia/20/1999 (H1N1) or B/Malaysia/2506/2004 influenza strains with Fluarix or placebo
5.  Of the 22 additional cases, 18 were unmatched and 4 were untyped; 15 of the 22 cases were A (H3N2) (11 cases with Fluarix and 4 cases with placebo).
Protection against severity of influenza or sequelae (pneumonia) in those with vaccine breakthrough infection was not demonstrated.

**Paediatric Study**

The immunogenicity and safety of a Fluarix 0.50 mL dose in children from 6 months to 35 months of age was evaluated in a multi-center, randomized, observer blind study, with 3 groups. 1 group receiving 0.50 mL of Fluarix (n=1065), 1 group receiving 0.25 mL of Fluarix (n=1069) and 1 group receiving 0.25 mL of a comparator flu vaccine (n=1074). Immunogenicity was determined by measuring haemagglutination inhibition antibody (HI) titres in serum samples at Day 0 (pre-vaccination) and at approximately Day 28 (for primed participants) or Day 56 (for unprimed participants). Table 2 shows a comparison of the Geometric Mean Titres from the Fluarix groups.

**Table 2: Comparison of Fluarix 0.50 mL dose versus Fluarix 0.25 mL dose in terms of Geometric Mean Titres (Adjusted GMT ratio) at post-vaccination (Day 28 or 56) for each strain (ATP cohort for immunogenicity)**

<table>
<thead>
<tr>
<th>Vaccine strain</th>
<th>Fluarix 0.50 mL</th>
<th>Fluarix 0.25 mL</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Adjusted GMT</td>
<td>N</td>
</tr>
<tr>
<td>A/Brisbane</td>
<td>1013</td>
<td>129.8</td>
<td>1017</td>
</tr>
<tr>
<td>A/Uruguay</td>
<td>1013</td>
<td>163.5</td>
<td>1017</td>
</tr>
<tr>
<td>B/Brisbane</td>
<td>1013</td>
<td>183.3</td>
<td>1017</td>
</tr>
</tbody>
</table>

1. Adjusted GMT = geometric mean antibody titer adjusted for baseline titer
2. N = Number of participants with both pre-and post-vaccination results available
3. 95% CI = 95% confidence interval for the adjusted GMT ratio (Ancova model: adjustment for baseline titer pooled variance); LL = lower limit, UL = upper limit

In general, Fluarix 0.50 mL induced a higher immune response than Fluarix 0.25 mL. The two Fluarix dosages were shown to be well-tolerated in the entire study population of 6 months to 35 months and the percentages of participants with AEs after vaccination were similar across treatment groups.

**INDICATIONS**

Fluarix is indicated for the prevention of influenza caused by influenza virus types A and B.

The NHMRC currently recommends annual vaccination against influenza for the following groups:

All adults aged 65 years and over.

All Aboriginal and Torres Strait Islander people aged 15 years and over.
Adults and children (≥ 6 months old) with conditions predisposing to severe influenza e.g.

- Cardiac disease including cyanotic congenital heart disease, coronary artery disease and congestive heart disease,

- Chronic respiratory conditions including:
  - suppurative lung disease, bronchiectasis, cystic fibrosis
  - chronic obstructive pulmonary disease and chronic emphysema
  - severe asthma defined as requiring frequent hospital visits,

- Other chronic illnesses requiring regular medical follow-up or hospitalisation including:
  - diabetes mellitus
  - chronic metabolic diseases
  - chronic renal failure
  - haemoglobinopathies
  - impaired immunity (including drug-induced immune impairment),

- Chronic neurological conditions (e.g. multiple sclerosis, spinal cord injuries, seizure disorders or other neuromuscular disorders) that can compromise respiratory function or expulsion of respiratory secretions or that can increase the risk for aspiration,

- People with impaired immunity including HIV,

- Long-term aspirin use in children, aged 6 months to 10 years,

- Pregnant women. It is recommended that influenza vaccine be offered in advance to women planning a pregnancy, and to women who will be in the second or third trimester of pregnancy during the influenza season, including those in the first trimester at the time of vaccinations,

- Residents of nursing homes and other long term care facilities, and

- Homeless people and those providing care to them.

People who may potentially transmit influenza to those at high risk of complications from influenza e.g.

- Staff of nursing homes,

- Health care providers,
• Staff of long-term care facilities, and
• Household contacts (including children ≥ 6 months old) of individuals in high-risk groups.

People involved in the commercial poultry industry or in culling poultry during confirmed avian influenza activity.

People providing essential services.

Workers in other industries if judged to be cost-saving.

Travellers (including any person who wishes to reduce the chance of becoming infected with influenza, and those at increased risk). Persons vaccinated with the previous season’s vaccine before travel should be revaccinated in the autumn with the current vaccine.

CONTRAINDICATIONS
Fluarix should not be administered to participants with known hypersensitivity to egg proteins (eggs, chicken feathers), gentamicin or any other excipient or residue of the vaccine.

As with other vaccines, the administration of Fluarix should be postponed in participants suffering from acute severe febrile illness (fever > 38.5°C). The presence of a minor illness with or without fever should not contraindicate the use of Fluarix.

PRECAUTIONS
Fluarix should under no circumstances be administered intravenously.

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

Immunisation can be affected by concomitant immunosuppressive therapy or an existing immunodeficiency.

Fluarix should be administered subcutaneously to participants with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these participants.
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.

Patients with a history of Guillain-Barré 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 coincidently developing the syndrome following influenza vaccination may be higher than in individuals with no history of GBS.

Fluarix will only prevent disease caused by influenza viruses of the types specified. Infections with other agents causing flu-like symptoms are not prevented by the vaccine.

Use in Pregnancy (Category B1)

In a reproductive and developmental toxicity study in which female rats received intramuscular injections of Fluarix at 8 times the clinical dose of haemagglutinin (based on mg/m²), 28 days prior to mating and at 4 times during the period of gestation, there were no significant toxicological effects on the dams, or their foetuses or pups. Circulating anti-H1N1 antibodies were detected in foetuses, demonstrating transfer of antibodies via the placental blood.

The safety of Fluarix when administered to pregnant women has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive and developmental toxicity. Fluarix should be used during pregnancy only when clearly needed, and the possible advantages outweigh the potential risks for the foetus.

The NHMRC states that influenza vaccine is safe for pregnant women. There is evidence from a number of studies that pregnant women, particularly during the second and third trimester, are at increased risk of influenza-associated complications. The NHMRC therefore recommends that all women who will be in the second or third trimester of pregnancy during the influenza season be vaccinated in advance, so that they will be protected during that period.

Use in Lactation
The safety of Fluarix when administered to breastfeeding women has not been evaluated. In rats, after maternal injection of Fluarix, antibodies against H1N1 were detected in dams, foetuses and pups during pregnancy and throughout lactation. These antibodies had no effects on pup development when assessed during lactation.

**Latex**

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

**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).

**INTERACTIONS WITH OTHER MEDICINES**

Fluarix can be administered simultaneously with other vaccines, however separate syringes and separate injection sites should be used.

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

**Fluarix should not be mixed with other vaccines in the same syringe.**

**ADVERSE EFFECTS**

**Clinical trial data**

Fluarix is well tolerated.

In controlled clinical studies, Fluarix was administered to more than 23,700 participants aged 18 years of age and older and to more than 8,600 participants from 6 months to 18 years of age. Signs and symptoms were solicited in all participants for a maximum of seven days following the administration of the vaccine. A checklist was used for this purpose.
In the studies with adult subjects, vaccinees were requested to report any clinical events occurring in the 21-day post-vaccination follow-up period. For studies with paediatric subjects, any clinical events were requested to be reported within the 28-day post-vaccination follow-up period.

Adverse reactions reported are listed according to the following frequency:

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

**Adults aged ≥ 18 years**

**Metabolism and nutrition disorders**
Very common: appetite loss

**Psychiatric disorders**
Very common: irritability

**Nervous system disorders**
Very common: drowsiness, headache

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

**Skin and subcutaneous tissue disorders**
Common: sweating

**Musculoskeletal and connective tissue disorders**
Very common: myalgia
Common: arthralgia

**General disorders and administration site conditions**
Very common: pain at the injection site, fatigue
Common: redness, swelling and induration at the injection site, shivering
Uncommon: fever, ecchymoses

**Children aged 6 months to < 18 years**

**Metabolism and nutrition disorders**
Very common: appetite loss

**Psychiatric disorders**
Very common: irritability

**Nervous system disorders**
Very common: drowsiness, headache

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

**Skin and subcutaneous tissue disorders**
Common: sweating

**Musculoskeletal and connective tissue disorders**
Very common: myalgia
Common: arthralgia

General disorders and administration site conditions
Very common: pain, redness and swelling at the injection site, fatigue
Common: induration at the injection site, shivering, fever
Uncommon: ecchymoses

1 only reported in subjects 6 months to < 6 years old

Post-Marketing Surveillance
Neurological disorders may have a temporal association with influenza vaccination, but no causal relationship has been established. An association between the A/New Jersey/76 swine influenza and Guillain-Barré Syndrome (GBS) has been demonstrated. More recently, an association between GBS and the influenza vaccines used in the Northern Hemisphere in the 1992-3 and 1993-4 seasons has been reported. Even with an estimated excess risk of 1 to 2 GBS cases per million persons vaccinated, this risk is still substantially smaller than the risk of severe influenza illness and its complications.

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, rash, angioedema

General disorders and administration site conditions
Rare: influenza-like illness, malaise

DOSAGE AND ADMINISTRATION

DOSAGE
One dose is sufficient for persons previously exposed to viruses of similar antigenic composition to the strain(s) present in the vaccine. Children aged under 9 years who are receiving the influenza vaccine for the first time, are recommended two doses of vaccine separated by an interval of at least 4 weeks. The vaccine should be administered by deep subcutaneous injection.

Adults and children 3 years and over: 0.5 mL
Children, 6 months to 35 months: 0.25 mL*
*When 0.5 mL doses were administered to children aged between 6 months to 35 months inclusive in a clinical study, the percentage of adverse events observed was similar to children receiving a 0.25 mL dose (See CLINICAL TRIALS).

Note: Influenza vaccine should be administered to children under 5 years of age with care and preferably only if they have a chronic debilitating disease, especially those with chronic cardiac, pulmonary, renal and metabolic disorders.

ADMINISTRATION
Fluarix can be administered intramuscularly or subcutaneously. THE VACCINE SHOULD NEVER BE ADMINISTERED INTRAVENOUSLY.

In patients with thrombocytopenia or bleeding disorders the vaccine should be administered subcutaneously.

INSTRUCTIONS FOR USE
Instructions for administration of 0.5 mL of the vaccine for use in adults and children 3 years and over
When a 0.5 mL dose is indicated, the entire content of the syringe should be injected.

Vaccines should be inspected visually for any foreign particulate matter and/or variation of physical aspects prior to administration. Before use, the vaccine should be well shaken to obtain a colourless to slightly opalescent liquid. Discard if the contents appear otherwise.

Instructions for administration of 0.25 mL of the vaccine for use in children from 6 months to 35 months
A marking line on the pre-filled syringe indicates a volume of 0.25 mL.

When a dose of 0.25 mL dose is indicated, the pre-filled syringe should be held in an upright position and half of the volume should be eliminated until the stopper reaches the marking line printed on the syringe. The remaining volume of 0.25 mL in the syringe should be injected.

Any unused product or waste material should be disposed of in accordance with local requirements.
VACCINATION SCHEDULE
Fluarix should be administered before the beginning of the influenza season or as required by the epidemiological situations. Vaccination should be repeated every year with an age-appropriate dose of vaccine of updated antigen composition.

Fluarix is for single use only. Discard any remaining contents.

PRESENTATION AND STORAGE CONDITIONS
Fluarix is presented in prefilled syringes.

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

Fluarix 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 is 12 months from the date of manufacture if stored between temperatures of +2°C and +8°C.

NAME AND ADDRESS OF THE SPONSOR
GlaxoSmithKline Australia Pty Ltd
Level 4, 436 Johnston Street,
Abbottsford, Victoria, 3067, Australia

POISON SCHEDULE OF THE DRUGS
Schedule 4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 13 October 2008

Date of most recent amendment: 22 November 2016

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