Registration No.: 2C 7/42 (N)

Importer / Manufacturer: Sanofi Pasteur Ltd., Thailand / Sanofi Pasteur Inc., USA

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICAL PRODUCT: FLUZONE, Influenza virus vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluzone®, Trivalent Anti-influenza Vaccine types A and B, a virus vaccine against influenza (purified by zone centrifugation, subvirion) for intramuscular use, a sterile suspension prepared from influenza viruses propagated in chicken embryos. The virus-containing liquids are harvested and inactivated with formaldehyde. The influenza virus is concentrated and purified in a lineal sucrose density gradient solution using a continuous flow centrifuge.

Then, the virus is chemically disrupted using polyethylene glycol pisoctylphenol ether (Triton® X-100, which belongs to the Union Carbide company) to produce a "split antigen" (subvirion). The virus unit (subvirion) is further purified using chemical procedures and suspended in a sodium phosphate-buffered isotonic sodium chloride solution.

The Fluzone vaccine for the 2011-2012 influenza season has been standardized according to United States Public Health Service requirements to contain 45 micrograms (µg) of hemagglutinin (HA) per 0.5 ml dose, in the recommended proportion of 15 µg of HA for each of the three types of the following strains: A/California/7/2009 X-179A (H1N1), A/Victoria/210/2009 X-187 (H3N2) and B/Brisbane/60/2008.

NO ANTIBIOTICS ARE USED IN THE MANUFACTURE OF THIS VACCINE.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Suspension for injection

After shaking the syringes or vials well, the Fluzone vaccine is essentially clear with a slightly opalescent color.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The Fluzone vaccine is instructed for use in persons 6 months of age and older for immunization against diseases caused by influenza virus types A and B contained in the vaccine.

The anti-influenza vaccine (subvirion) is highly recommended for any person 6 months of age or older, who, because of age or medical condition, has a greater risk of complications from influenza.

Also, medical personnel and others (including family members) in close contact with high-risk persons should be vaccinated to decrease the risk of the infection being transmitted to them. The vaccine may also be administered to a person wishing to reduce the possibility of contracting
influenza or who is at risk of transmitting influenza to others. The recommended dose of the vaccine for the 2011-2012 season is in the Dose and Administration section. The instructions for using the vaccine with certain groups of persons are given below.

VACCINE REMAINING FROM THE YEAR 2010-2011 SHOULD NOT BE USED TO PROVIDE PROTECTION DURING THE 2011-2012 INFLUENZA SEASON.

In order to avoid losing opportunities for vaccinating persons at high risk of serious influenza-related complications, these persons should be offered the vaccine as soon as it is available, when they visit health centers for routine check-ups or in the event that they are hospitalized. The United States Advisory Committee on Immunization Practices (ACIP) recommends vaccinating all persons 6 months of age or older, including those with an increased risk of complications related to influenza, those having household contact with high-risk persons, and health workers.

Although the current anti-influenza vaccine may contain one or more antigens administered in previous years, annual vaccination is necessary because some antigens change every year, and because immunity decreases in the year following vaccination. The vaccine prepared for the preceding year should not be administered for the purpose of providing protection during the current influenza season.

The use of the intramuscular route is recommended for its administration. Adults and older children should be injected in the deltoid muscle, and infants and young children should be injected in the anterolateral aspect of the thigh.

VACCINATION GROUPS
Persons with High Risk of Complications Caused by Influenza. According to the ACIP, vaccination is recommended for all persons 6 months of age and older, including the following groups who are at higher risk of presenting with complications caused by influenza:
• Persons 50 years of age or older;
• Residents of nursing homes and other extended-care facilities presenting with chronic medical conditions, regardless of their age;
• Adults and children suffering from chronic heart or lung diseases, including asthma;
• Adults and children who required continuous medical attention or hospitalization over the past year as a result of chronic metabolic diseases, (including diabetes mellitus), renal insufficiency, hematologic disorders, or immunosuppression (including immunosuppression caused by medications or by the human immunodeficiency virus [HIV]);
• Infants, children, and adolescents (6 months to 18 years of age) undergoing prolonged treatment with acetylsalicylic acid. This treatment can increase the risk of Reye's syndrome after having influenza;
• Adults and children who have any condition (for example, cognitive dysfunctions, spinal cord lesions, convulsive disorders or other neuromuscular disorders) that can compromise respiratory function or management of respiratory secretions, or that may increase the risk of aspiration;
• Women who will be pregnant during influenza season; and
• Children from 6 to 59 months of age (that is, 6 months to 4 years).

Persons from 50 to 64 years of age
The vaccination is also recommended for persons from 50 to 64 years of age, as this group presents an increased prevalence of high-risk chronic medical conditions. Persons who smoke tobacco products also have a high risk of presenting with influenza-related
complications, and should, therefore, be immunized. Persons from 50 to 64 years of age without high risk conditions also receive benefits from vaccination, such as lowered absenteeism from work, a decrease in diseases due to influenza, and a decrease in medical office visits and medication, including antibiotics.

Persons who May Transmit Influenza to High Risk Individuals
Persons who have clinical or subclinical influenza infections can transmit influenza to those at high risk. Efforts to protect members of high-risk groups can improve if opportunities for exposure to influenza originating in health care workers are decreased. For this reason, we recommend that the following persons be vaccinated:

- Doctors, nurses, and other employees of hospitals or any other health care facility;
- Employees of retirement homes and extended care facilities who have contact with the patients or retirees;
- Employees of institutions providing assistance with daily activities to persons in the high-risk group;
- Home care providers for high-risk persons; and
- Persons (including children) living under the same roof as high-risk individuals.

In addition, since children from 0 to 59 months of age have an increased risk of influenza-related hospitalizations, vaccination is recommended for their contacts and care givers. Particularly if the care givers are in contact with children from 0 to 5 months of age, as influenza vaccines have not been approved by the United States Food and Drug Administration (FDA) for use with children under 6 months of age.

Other Persons
Doctors should administer the vaccine to any persons wishing to reduce their risk of contracting the infection (the vaccine may be administered to children from 6 months of age). In order to prevent interruption of essential public services when an epidemic arises, vaccination programs directed at public service providers may be implemented. Students and those who live in residential institutions (e.g., student dormitories) should also be vaccinated to impede the interruption of their routine activities during epidemics.

Healthy Children
Clinical studies indicate hospitalization rates are higher in younger children as compared to older children when the influenza virus is in circulation. These hospitalization indexes are comparable with those of other groups considered to be at high risk of influenza-related complications.

Two recent studies have attempted to separate out the effects of the respiratory sinus virus from those of the influenza virus in terms of the hospitalization rates in children without high-risk conditions. Both studies reported that children under 2 years of age, and, possibly those from 2 to 4 years of age, considered to be healthy, have an increased risk of influenza-related hospitalization when compared with older children. Some studies report that trivalent inactivated influenza vaccine decreases acute influenza-associated otitis media by up to approximately 30% in small children.

Since children between 6 and 59 months of age are at a substantially increased risk of influenza related hospitalizations, the ACIP, the American Academy of Pediatrics, and the American Academy of Family Physicians recommend vaccination of all children in this age group. The ACIP currently recommends vaccination against influenza for all persons 6 months of age and older, including those with or without medical indications of high risk.

Pregnant Women
Because of the increased risk of influenza-related complications, the ACIP recommends that women who will be pregnant during influenza season be vaccinated. A study of influenza
vaccination in over 2,000 women showed no findings of adverse fetal effects related to this vaccine. (see Pregnant women, Category C).

**Breastfeeding**
It is not known if the antigens in the Fluzone vaccine are excreted in human milk. Since many drugs are excreted in mothers' milk, precautions should be taken when administering Fluzone to women who are nursing.

**Persons infected with Human Immunodeficiency Virus (HIV)**
There is little information available with regard to the frequency and seriousness of influenza or about the benefits of anti-influenza vaccine in persons infected with HIV. However, a recent retrospective study with young and middle-aged women found that the attributable risk of hospitalizations resulting from cardiopulmonary problems among women infected with HIV was higher during influenza season than in peri-influenza periods. The hospitalization risk for women infected with HIV was greater than the risk for women with other identified high-risk conditions due to complications of influenza, including chronic heart and lung diseases. Other reports indicate that in some persons infected with HIV, influenza symptoms can be prolonged and the risk of complications due to influenza can increase.
The anti-influenza vaccine has substantially stimulated the production of levels of anti-influenza antibodies in persons infected with HIV who are vaccinated, who show few signs of Acquired Autoimmune Deficiency, and who have high levels of T CD4+ lymphocytes. However, in patients with advanced stages of AIDS who have low numbers of T CD4+ lymphocytes, the anti-influenza vaccine might not induce levels of protective antibodies; a second dose of the vaccine does not improve the immune response in these persons.
One study discovered that, in a patient infected with AIDS, levels of the HIV RNA increased transitorily after the anti-influenza vaccine. Some studies have demonstrated a temporary (e.g. from 2 to 4 weeks) increase in HIV-1 replication in the plasma or monocytes in the peripheral blood of the person infected with HIV, after the administration of the vaccine; other studies using similar laboratory techniques have not documented any significant increase in HIV replication. Decrease in the number of T CD4+ lymphocytes and the progression of the disease have not been demonstrated in HIV-infected person who receive the vaccine. There is little information available on the effect of antiretroviral therapy on the potential increase in levels of HIV RNA after a natural influenza infection or the anti-influenza vaccination. Since influenza can cause serious illnesses, and considering that the anti-influenza vaccine can produce levels of protective antibodies, vaccination will benefit many patients infected with HIV, including pregnant women infected with HIV.

**Travelers**
The risk of exposure to influenza during a trip depends on the time of year and the geographic destination. In tropical countries, influenza can occur at any time of year, although in the temperate regions of the southern hemisphere, the greatest activity takes place from April to September. In temperate climate zones in the northern and southern hemispheres, travelers can find themselves exposed to the influenza virus in the summer as well, especially when they travel in organized tourist groups with people from different parts of the world where influenza viruses might be circulating.
Those at the highest risk of presenting complications of influenza, and who did not receive an antineumflueza vaccination during the previous fall or winter, should consider getting this vaccination before traveling if they are planning to travel: a) to tropical countries; b) at any time of year with an organized tourist group; or c) to the southern hemisphere between April and September. Persons at high risk who received the vaccination for the previous season before their departure should be revaccinated with the most recent vaccine as soon as it is available.
Because the anti-influenza vaccine might not be available in North America during the summer, it is advisable that those persons who are at higher risk consult their physicians with regard to the symptoms and risks of influenza and the appropriateness of taking antiviral medications with them for prophylaxis or for anti-influenza treatment before traveling during the summer.

**PEDIATRIC USE**

*THE SAFETY AND EFFECTIVENESS OF THE FLUZONE VACCINE (SUBVIRION) IN CHILDREN UNDER 6 MONTHS OF AGE HAS NOT BEEN ESTABLISHED.*

The ACIP recommends that all healthy children 6 months of age and older, and close contacts of children from 0 to 59 months of age be vaccinated against influenza.

### 4.2 Posology and method of administration

Whenever the packaging permits, medications for injections should be inspected visually to ensure that they do not contain particles and are not discolored. If these conditions are present, the vaccine should not be used.

**Shake the syringe or vial with the vaccine well before administering it. The prefilled 0.25 ml syringe should be the presentation of preference when a dose of 0.25 ml is indicated for small children.**

**Do NOT inject intravenously.**

The anti-influenza vaccine should be offered for administration as soon as it is available.

**Children**

Based on current ACIP recommendations, unvaccinated or incompletely vaccinated children from 6 to 35 months of age should receive two 0.25 ml doses, one on Day 1 followed by another 0.25 ml dose at least 1 month later.

All children from 6 to 35 months of age should receive one single dose of 0.25 ml.

Unvaccinated or incompletely vaccinated children from 36 months to 8 years of age should receive two 0.5 ml doses (based on current ACIP recommendations), one on Day 1 followed by another 0.5 ml dose at least 1 month later.

All children from 36 months to 8 years of age should receive one single dose of 0.5 ml. Children 9 years of age and older should receive one single intramuscular dose of 0.5 ml.

There are recommendations available for needle length for the different age groups. For needle length, refer to the recommendation of the Advisory Committee on Immunization Practices (ACIP).

For children over 36 months of age, the deltoid muscle should be used; for children under 36 months, the anterolateral aspect of the thigh should be used.

**Adults**

The Fluzone vaccine should be administered as one single intramuscular dose of 0.5 ml, preferably in the deltoid muscle.

The vaccine should not be injected into the gluteal region or in areas where they might be a major nerve trunk.
The Fluzone vaccine should be used on persons over 6 months of age. Fluzone is NOT approved for infants under 6 months of age.

4.3 Contraindication

Systemic hypersensitivity reactions to egg proteins (eggs or egg products), chicken protein, or any component of the Fluzone vaccine, or a life-threatening reaction after a previous administration of the vaccine or of a vaccine containing the same substances. Immunization should be postponed in patients with any active neurological disorder, but it should be considered after the process of the disease has stabilized.

4.4 Special warnings and precautions for use

WARNINGS
Recurrence of Guillain-Barré syndrome (GBS) has been temporarily associated with the administration of the anti-influenza vaccine. The Fluzone vaccine should be administered to persons who have a previous history of Guillain-Barré only on the basis of a careful examination of the possible benefits and risks.

The Fluzone vaccine should not be administered to a person with a known systemic hypersensitivity reaction after a previous administration of any anti-influenza vaccine or any component of the vaccine (e.g., eggs or egg products) as defined in the Description.

If the Fluzone vaccine is used with persons whose production of antibodies is deficient because of genetic defects, immunodeficiency disease, or immunosuppressive therapy, the desired immune response may not take place.

As with any other vaccine, the Fluzone vaccination may not protect 100% of susceptible individuals.

PRECAUTIONS
GENERAL
Medical personnel should take appropriate precautions for the safe and effective use of this vaccine.

Because the intramuscular injection can cause a hematoma at the injection site, the Fluzone vaccine should not be administered to persons with bleeding disorders, such as hemophilia or thrombocytopenia, or to persons undergoing anticoagulant therapy, unless the possible benefits are clearly superior to the risk of administration. If the decision is made to administer the Fluzone vaccine to these persons, it should be administered with care, taking measures to avoid the risk of formation of a hematoma following the injection.

As a precautionary measure, an injection of epinephrine chlorhydrate (1:1000) should be immediately available in the event of serious unexpected allergic reactions or anaphylactic reactions.

The influenza virus behaves in a totally unpredictable fashion with respect to major antigen changes that can be experienced from time to time. It has been definitively established that the anti-influenza vaccine, in its current form, is not effective against all possible influenza strains. Most individuals are protected against the strains of the virus from which the vaccine has been prepared or against closely related strains.

Immunization should be postponed in patients with active respiratory infections that present with fever.

Because convulsions associated with fever are greater in children from 6 to 35 months of age, special care should be taken in evaluating the risks and benefits of vaccination in these patients.
Before injecting any vaccination, it is advisable to take all known precautions to avoid secondary effects. The idea is basically to examine the patients' medical histories in order to ensure that they are not sensitive to the vaccine or a similar vaccine, and to review their immunization histories and current state of health, as well as to become familiar with recent literature on the vaccine that is to be used. Precautions should be taken so as not to inject the vaccine into a blood vessel. New, sterile, syringes and needles should be used for every patient in order to prevent transmission of hepatitis or any other infectious agent from one person to another. Needles should be disposed of appropriately.

INFORMATION FOR THE PATIENT
Patients, parents, or guardians should be instructed by medical personnel on the risks and benefits of vaccination against influenza; they should also report any serious secondary effects to medical personnel.

4.5 Interaction with other medical products and forms of interaction

SIMULTANOUS USE WITH THE PNEUMOCOCCAL VACCINE.
It has been demonstrated in clinical studies with adults that the simultaneous use of Fluzone and the pneumococcal vaccine is safe when they are administered with different syringes and in anatomically different body parts. Although some patients are recommended to be vaccinated annually with the anti-influenza vaccine, pneumococcal vaccine should be administered only once. No studies have been done on the concomitant administration of the inactivated influenza vaccine and the other vaccines that are routinely administered during childhood. According to the ACIP, inactivated vaccines do not usually interfere with the immune response to other inactivated or active vaccines, and children may receive the anti-influenza vaccine at the same time that they get the other usual vaccinations.

Interactions with other medications.
Although vaccination against influenza can inhibit the clearance of drugs such as warfarin, theophylline, and phenytoin, and affect medications based aminopyridines, there have been no reports of secondary reactions caused by these medications on patients vaccinated with the antiinfluenza vaccine. If the Fluzone vaccine is administered to immunocompromised persons, or to those who are receiving immunosuppressant therapy, the expected immune response may not occur. This includes patients with an asymptomatic AIDS or AIDS-Related Complex infection, or severe combined immune deficiency, hypogammaglobulinemia, or agammaglobulinemia; patients having an altered immune response caused by diseases such as leukemia, lymphoma, generalized tumors, or an immune system affected by treatment with corticosteroids, alkylating agents, antimetabolics, or radiation.

4.6 Pregnancy and lactation

CATEGORY C PREGNANCY
No studies on reproduction in animals have been done with this vaccine. It is not known if the vaccine can cause fetal damage when administered to a pregnant woman, or if it can affect reproductive capacity. Information on the use of this vaccine in pregnant women is limited. The Fluzone vaccine should be administered to pregnant women after the risks and benefits are evaluated.
4.7 Effects on the ability to drive and use machines

4.8 Undesirable effects

When patients are educated about the potential collateral effects, emphasis should be placed on the following: 1) the inactivated anti-influenza vaccine contains dead, non-infectious viruses and cannot cause influenza; and 2) that coincidences with respiratory diseases not related to the anti-influenza vaccine can occur after vaccination.

Local reactions
In placebo-controlled studies among adults, the most frequent adverse effect of the vaccination was soreness at the injection site (affecting 10% - 64% of patients) that lasted less than two days, of localized soreness and swelling. These local reactions tend to be mild and rarely interfere with the person's ability to conduct usual daily activities.

Systemic reactions
Fever, general discomfort, myalgia, and other systemic symptoms can occur after vaccination, and the majority of these affect persons with no prior exposure to the influenza virus antigens in the vaccine (e.g., small children). These reactions begin 6-12 hours after the vaccination and can persist for 1-2 days. Recent placebo-controlled trials demonstrate that among older persons and young healthy adults, the administration of the split virus anti-influenza vaccine is not associated with higher rates of systemic symptoms (e.g. fever, general discomfort, myalgia, and headache) when compared with placebo injections.

Post-marketing experience
The following events were reported during the period after the use of the Fluzone vaccine was approved. As these events were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency, or to establish a causal relationship with respect to exposure to the vaccine.

Blood and Disorders of the lymphatic system: Thrombocytopenia, lymphadenopathy.

Immune system disorders: Anaphylaxis, other allergic/hypersensitivity reactions (including urticaria and angioedema).

Nervous system disorders: Guillain-Barré Syndrome (GBS), convulsions, myelitis (including encephalomyelitis and transversal myelitis), facial paralysis (Bell's paralysis), optic neuritis/neuropathy, brachial neuritis, syncope (immediately after the vaccination), vertigo, paresthesia.

Vascular disorders: Vasculitis, vasodilation/flushing.

Respiratory, thoracic, and mediastinal disorders: Dyspnea, pharyngitis, rhinitis.

Disorders of the skin and subcutaneous tissue: Stevens-Johnson Syndrome.

General discomfort and conditions at the administration site: Fever, soreness, pruritis, asthenia/fatigue, pain in the extremities, chest pain.
Other adverse events associated with the anti-influenza vaccine
Anaphylaxis has been reported after the administration of anti-influenza vaccines. Although the Fluzone vaccine contains only a limited quantity of egg protein, this protein can cause immediate hypersensitivity reactions among persons with severe allergies to eggs. Allergic reactions including urticaria, angioedema, allergic asthma, and systemic anaphylaxis.

The 1976 anti-swine flu vaccine was associated with an increase in the frequency of Guillain-Barré Syndrome (GBS). Evidence for a causal relationship of GBS and subsequent vaccines prepared from other influenza viruses is unclear. If the anti-influenza vaccine does pose a risk, it is probably slightly higher than 1 additional case/1 million vaccinated persons.

Neurological disorders temporarily associated with the vaccination against influenza have been reported, such as encephalopathy, optic neuritis/neuropathy, partial facial paralysis, and neuropathy of the brachial plexus.

Microscopic polyangitis (vasculitis) temporarily associated with anti-influenza vaccination has been reported.

4.9 Overdose

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

5.2 Pharmacokinetic properties

5.3 Preclinical safety data

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Thimerosal is not used in the process of manufacturing the single-dose presentations of preservative free Fluzone vaccine. The Fluzone vaccine is available in an additional presentation: a multi-dose vial containing 5 ml of the vaccine. This contains thimerosal, a mercury derivative added as a preservative. Every 0.5 ml dose contains 25 µg of mercury. Gelatin is added at 0.05% as a stabilizer.

6.2 Incompatibilities

6.3 Shelf life

1 year

6.4 Special precautions for storage

Store refrigerated at between +2°C and +8°C (35°F and 46°F). Freezing destroys the activity of this product. Therefore, NEVER USE FLUZONE VACCINE THAT HAS BEEN FROZEN
6.5 Nature and contents of container

The Fluzone vaccine is available in three preservative-free presentations: a prefilled syringe containing 0.25 ml (for pediatric use, for children from 6 to 35 months of age) distinguished by a pink syringe plunger rod, a prefilled syringe and vial containing 0.5 ml (for persons 36 months of age or older).

- Prefilled syringe, 0.25 ml (contains no preservatives) (shake well before using), for single dose application.
- Prefilled syringe, 0.5 ml (contains no preservatives) (shake well before using), for single dose application.
- Vial, 0.5 ml (contains no preservatives) (shake well before using), for single dose application.
- Vial, 5.0 ml, for administration with syringe and needle (contains preservatives) (shake well before extracting a dose) for multi-dose application.

6.6 Special precautions for disposal and other handling

7. **MARKETING AUTHORISATION HOLDER**
Sanofi Pasteur Ltd., Bangkok, Thailand

8. **MARKETING AUTHORISATION NUMBER(S)**
2C 7/42 (N)

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
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10. **DATE OF REVISION OF THE TEXT**
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(The above information is based on the currently approved leaflet)