## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use FLULAVAL safely and effectively. See full prescribing information for FLULAVAL.**

**FLULAVAL (Influenza Virus Vaccine)**
**Suspension for Intramuscular Injection**
**2011-2012 Formula**
**Initial U.S. Approval: 2006**

### ----------INDICATIONS AND USAGE----------

- FLULAVAL is a vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. FLULAVAL is approved for use in persons 18 years of age and older. (1)
- This indication is based on immune response elicited by FLULAVAL, and there have been no controlled trials adequately demonstrating a decrease in influenza disease after vaccination with FLULAVAL. (1, 14)

### ---------- DOSAGE AND ADMINISTRATION ----------

A single 0.5-mL intramuscular injection. (2.2)

### ---------- DOSAGE FORMS AND STRENGTHS ----------

FLULAVAL is a suspension in 5-mL multi-dose vials containing 10 doses (each dose is 0.5 mL). (3)

### ----------CONTRAINDICATIONS----------

Known severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine including egg protein or to a previous dose of any influenza vaccination. (4, 11)

### ---------- WARNINGS AND PRECAUTIONS ----------

- If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give FLULAVAL should be based on careful consideration of the potential benefits and risks. (5.1)
- Immunosuppressed persons may have a reduced immune response to FLULAVAL. (5.2)

### ---------- ADVERSE REACTIONS ----------

The most common (≥10%) solicited injection site reactions were pain (51%), redness (13%), and/or swelling (11%); the most common solicited systemic adverse events were fatigue (20%), headache (18%), and myalgia/arthralgia (18%). (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.**

### ----------DRUG INTERACTIONS----------

Do not mix with any other vaccine in the same syringe or vial. (7.1)

### ---------- USE IN SPECIFIC POPULATIONS ----------

- Safety and effectiveness of FLULAVAL have not been established in pregnant women, nursing mothers, or children. (8.1, 8.3, 8.4)
- Register women who receive FLULAVAL while pregnant in the pregnancy registry by calling 1-888-452-9622. (8.1)
- Geriatric Use: Antibody responses were lower in geriatric subjects than in younger subjects. (8.5)

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 06/2011**

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## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

FLULAVAL® is indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. FLULAVAL is approved for use in persons 18 years of age and older.

This indication is based on immune response elicited by FLULAVAL, and there have been no controlled trials adequately demonstrating a decrease in influenza disease after vaccination with FLULAVAL *[see Clinical Studies (14)]*.

## 2 DOSAGE AND ADMINISTRATION

For intramuscular administration only.

### 2.1 Preparation for Administration

Shake the multi-dose vial vigorously each time before withdrawing a dose of vaccine. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

Between uses, return the multi-dose vial to the recommended storage conditions, between 2º and 8ºC (36º and 46ºF). Do not freeze. Discard if the vaccine has been frozen. Once entered, a multi-dose vial, and any residual contents, should be discarded after 28 days.

It is recommended that small syringes (0.5-mL or 1-mL) be used to minimize any product loss.

### 2.2 Recommended Dose and Schedule

FLULAVAL should be administered as a single 0.5-mL injection by the intramuscular route preferably in the region of the deltoid muscle of the upper arm.

Do not administer this product intravenously, intradermally or subcutaneously.

## 3 DOSAGE FORMS AND STRENGTHS

FLULAVAL is a suspension available in 5-mL multi-dose vials containing 10 doses (each dose is 0.5 mL).

## 4 CONTRAINDICATIONS

Do not administer FLULAVAL to anyone with known severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine including egg protein or to a previous dose of any influenza vaccination *[see Description (11)]*.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Guillain-Barré Syndrome

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza

vaccine, the decision to give FLULAVAL should be based on careful consideration of the potential benefits and risks.

### 5.2 Altered Immunocompetence

If FLULAVAL is administered to immunosuppressed persons, including individuals receiving immunosuppressive therapy, the immune response may be lower than in immunocompetent persons.

### 5.3 Persons at Risk of Bleeding

As with other intramuscular injections, FLULAVAL should be given with caution in individuals with bleeding disorders such as hemophilia or on anticoagulant therapy to avoid the risk of hematoma following the injection.

### 5.4 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions to allow an assessment of benefits and risks. Appropriate medical treatment, including epinephrine, and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

### 5.5 Limitations of Vaccine Effectiveness

Vaccination with FLULAVAL may not protect all susceptible individuals.

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine, and may not reflect the rates observed in practice. As with any vaccine, there is the possibility that broad use of FLULAVAL could reveal adverse events not observed in clinical trials.

In the largest clinical trial, the most common (≥10%) solicited injection site reactions were pain (51%), redness (13%), and/or swelling (11%); the most common solicited systemic adverse events were fatigue (20%), headache (18%), and myalgia/arthralgia (18%).

Safety data has been obtained from 3 randomized, controlled trials, one of which was a placebo-controlled efficacy study. In these trials, 9,836 subjects were randomized to receive either FLULAVAL (5,114 subjects in the safety analysis), FLUZONE, a US-licensed trivalent, inactivated influenza virus vaccine, manufactured by Sanofi Pasteur SA (894 subjects in the safety analysis), or placebo (3,828 subjects in the safety analysis), intramuscularly. In these studies, solicited events were collected for 4 days (i.e., 30 minutes post-vaccination through the next 3 days) using diary cards. Unsolicited adverse events that occurred within 22 days of vaccination (day 0-21) were recorded based on spontaneous reports or in response to queries about changes in health status.

Study 1 (Immunogenicity): Safety information was collected in a randomized, controlled US study. This study included 1,000 adults 18 to 64 years of age who were

randomized to receive FLULAVAL (N = 721) or a US-licensed trivalent, inactivated influenza virus vaccine (N = 279). Among recipients of FLULAVAL, 57% were female; 91% of subjects were white and 9% were of other racial/ethnic groups. The mean age of subjects was 38 years; 80% were 18 to 49 years of age and 20% were 50 to 64 years of age.

Study 2 (Immunogenicity Non-Inferiority): Safety information was collected in a randomized, double-blind, active-controlled US study. The study included 1,225 adults ≥50 years of age randomized to receive FLULAVAL (N = 610) or a US-licensed trivalent, inactivated influenza virus vaccine (N = 615). In the total population, 57% were female; 95% of subjects were white and 5% were of other racial/ethnic groups. The mean age of subjects was 66 years (46% were 50 to 64 years of age, 41% were 65 to 79 years of age, and 13% were ≥80 years of age).

Study 3 (Efficacy): Safety information was collected in a double-blind, placebo-controlled US study. The study included 7,658 adults 18 to 49 years of age randomized to receive FLULAVAL (N = 3,807) or placebo (N = 3,851). In the total population, 61% were female; 84% of subjects were white, 10% black, 2% Asian, and 4% were of other racial/ethnic groups. The mean age of subjects was 33 years.

Solicited Adverse Events: Solicited local adverse reactions and systemic adverse events collected for 4 days (day of vaccination and the next 3 days) are presented in Table 1.

**Table 1. Incidence of Solicited Local Adverse Reactions and Systemic Adverse Events in the First 4 Days After Administration of FLULAVAL, Comparator Influenza Vaccine[a], or Placebo (Total Vaccinated Cohort)**

| | Percentage of Subjects Reporting Event[b] | | | | | |
|---|---|---|---|---|---|---|
| | Study 1 (18 to 64 years of age) | | Study 2[c] (50 years of age and older) | | Study 3[c] (18 to 49 years of age) | |
| | FLULAVAL N = 721 | Comparator N = 279 | FLULAVAL N = 610 | Comparator N = 615 | FLULAVAL N = 3,783 | Placebo N = 3,828 |
| **Local** | | | | | | |
| Pain | 24 | 31 | 25 | 32 | 51 | 14 |
| Redness | 11 | 10 | 10 | 11 | 13 | 6 |
| Swelling | 10 | 10 | 7 | 9 | 11 | 3 |
| **Systemic** | | | | | | |
| Headache | 18 | 17 | 11 | 12 | 18 | 19 |
| Fatigue | 17 | 15 | 12 | 13 | 20 | 18 |
| Myalgia[d] | 13 | 16 | 11 | 10 | 18 | 10 |
| Fever (≥99.5°F) | 11 | 10 | 1 | 1 | 3 | 1 |
| Malaise | 10 | 10 | 6 | 7 | 9 | 6 |
| Sore throat | 9 | 9 | 5 | 6 | 9 | 9 |
| Reddened eyes | 6 | 5 | 4 | 7 | 7 | 6 |
| Cough | 6 | 7 | 5 | 6 | 8 | 7 |
| Chills | 5 | 2 | 3 | 6 | 4 | 4 |
| Chest tightness | 3 | 1 | 2 | 2 | 3 | 3 |
| Facial swelling | 1 | 1 | 1 | 2 | 1 | 1 |

[a] US-licensed trivalent, inactivated influenza virus vaccine (manufactured by Sanofi Pasteur SA).

[b] Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available.

[c] Study 2: NCT00232947; Study 3: NCT00216242.

[d] For Study 2 and Study 3, includes myalgia and arthralgia.

Unsolicited Adverse Events: The incidence of unsolicited adverse events in the 21 days post-vaccination was comparable for FLULAVAL and the active comparator in Study 1 (16% and 15%, respectively) and in Study 2 (18% and 21%, respectively). In Study 3, the incidence of unsolicited adverse events was comparable for the groups (21% for FLULAVAL and 19% for placebo).

Unsolicited adverse events defined as reported with FLULAVAL in >1.0% of subjects are described as follows: Study 1: Cough, headache, and pharyngolaryngeal pain; Study 2: Diarrhea, headache, and nasopharyngitis; and Study 3: Pharyngolaryngeal pain, headache, fatigue, cough, injection site pain, upper respiratory tract infection, musculoskeletal pain, nasopharyngitis, injection site erythema and discomfort.

Serious Adverse Events (SAEs): In Study 1, no SAEs were reported. In Study 2, 3% of subjects receiving FLULAVAL and 3% of subjects receiving the active comparator reported SAEs. In Study 3, 1% of subjects receiving FLULAVAL and 1% of subjects receiving placebo reported SAEs. In the 3 clinical trials, the rates of SAEs were comparable between groups and none of the SAEs were considered related to vaccination.

### 6.2 Postmarketing Experience

In addition to reports in clinical trials, the following adverse events have been identified during postapproval use of FLULAVAL. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their incidence rate or establish a causal relationship to the vaccine. Adverse events described here are included because: a) they represent reactions which are known to occur following immunizations generally or influenza immunizations specifically; b) they are potentially serious; or c) the frequency of reporting.

Blood and Lymphatic System Disorders: Lymphadenopathy.

Eye Disorders: Eye pain, photophobia.

Gastrointestinal Disorders: Dysphagia, vomiting.

General Disorders and Administration Site Conditions: Chest pain, injection site inflammation, asthenia, injection site rash, influenza-like symptoms, abnormal gait, injection site bruising, injection site sterile abscess.

Immune System Disorders: Allergic edema of the mouth, anaphylaxis, allergic edema of the throat.

Infections and Infestations: Rhinitis, laryngitis, cellulitis.

Musculoskeletal and Connective Tissue Disorders: Muscle weakness, arthritis.

Nervous System Disorders: Dizziness, paresthesia, hypoesthesia, hypokinesia, tremor, somnolence, syncope, Guillain-Barré syndrome, convulsions/seizures, facial or cranial nerve paralysis, encephalopathy, limb paralysis.

Psychiatric Disorders: Insomnia.

Respiratory, Thoracic, and Mediastinal Disorders: Dyspnea, dysphonia, bronchospasm, throat tightness.

Skin and Subcutaneous Tissue Disorders: Urticaria, localized or generalized rash, pruritus, sweating.

Vascular Disorders: Flushing, pallor.

### 6.3 Adverse Events Associated With Influenza Vaccines

Anaphylaxis has been reported after administration of FLULAVAL. Although FLULAVAL contains only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Allergic reactions include hives, angioedema, allergic asthma, and systemic anaphylaxis *[see Contraindications (4)]*.

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with subsequent vaccines prepared from other influenza viruses is unclear. If influenza vaccine does pose a risk, it is

probably slightly more than 1 additional case/1 million persons vaccinated.

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

Microscopic polyangitis (vasculitis) has been reported temporally associated with influenza vaccination.

# 7 DRUG INTERACTIONS

## 7.1 Concomitant Administration With Other Vaccines

There are no data to assess the concomitant administration of FLULAVAL with other vaccines. If FLULAVAL is to be given at the same time as another injectable vaccine(s), the vaccines should always be administered at different injection sites. FLULAVAL should not be mixed with any other vaccine in the same syringe or vial.

## 7.2 Immunosuppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to FLULAVAL.

# 8 USE IN SPECIFIC POPULATIONS

## 8.1 Pregnancy

Pregnancy Category B

A reproductive and developmental toxicity study has been performed in female rats at a dose approximately 56 times the human dose (on a mg/kg basis) and revealed no evidence of impaired female fertility or harm to the fetus due to FLULAVAL. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, FLULAVAL should be given to a pregnant woman only if clearly needed.

In a reproductive and developmental toxicity study, the effect of FLULAVAL on embryo-fetal and pre-weaning development was evaluated in pregnant rats. Animals were administered FLULAVAL by intramuscular injection once prior to gestation, and during the period of organogenesis (gestation days 6, 8, 11, and 15), 0.1 mL/rat/occasion (approximately 56-fold excess relative to the projected human dose on a body weight basis). No adverse effects on mating, female fertility, pregnancy, parturition, lactation parameters, and embryo-fetal or pre-weaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis.

Pregnancy Registry: GlaxoSmithKline maintains a surveillance registry to collect data on pregnancy outcomes and newborn health status outcomes following vaccination with FLULAVAL during pregnancy. Women who receive FLULAVAL during pregnancy should be encouraged to contact GlaxoSmithKline directly or their healthcare provider should contact GlaxoSmithKline by calling 1-888-452-9622.

### 8.3 Nursing Mothers

It is not known whether FLULAVAL is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FLULAVAL is administered to a nursing woman.

### 8.4 Pediatric Use

Safety and effectiveness of FLULAVAL in pediatric patients have not been established.

### 8.5 Geriatric Use

In clinical trials, there were 330 subjects who were ≥65 years of age and received FLULAVAL; 142 of these subjects were ≥75 years of age. Hemagglutination-inhibiting (HI) antibody responses were lower in geriatric subjects than younger subjects after administration of FLULAVAL. *[See Clinical Studies (14.2).]* Solicited adverse events were similar in frequency to those reported in younger subjects *[see Adverse Reactions (6.1)]*.

## 11 DESCRIPTION

FLULAVAL, Influenza Virus Vaccine, for intramuscular injection, is a trivalent, split-virion, inactivated influenza virus vaccine prepared from virus propagated in the allantoic cavity of embryonated hens' eggs. Each of the influenza virus strains is produced and purified separately. The virus is inactivated with ultraviolet light treatment followed by formaldehyde treatment, purified by centrifugation, and disrupted with sodium deoxycholate.

FLULAVAL is a sterile, translucent to whitish opalescent suspension in a phosphate-buffered saline solution that may sediment slightly. The sediment resuspends upon shaking to form a homogeneous suspension. FLULAVAL has been standardized according to USPHS requirements for the 2011-2012 influenza season and is formulated to contain 45 mcg hemagglutinin (HA) per 0.5-mL dose in the recommended ratio of 15 mcg HA of each of the following 3 strains: A/California/7/2009 NYMC X-181 (H1N1), A/Victoria/210/2009 NYMC X-187 (H3N2) (an A/Perth/16/2009-like virus), and B/Brisbane/60/2008. Thimerosal, a mercury derivative, is added as a preservative. Each dose contains 25 mcg mercury. Each dose may also contain residual amounts of egg proteins (≤1 mcg ovalbumin), formaldehyde (≤25 mcg), and sodium deoxycholate (≤50 mcg). Antibiotics are not used in the manufacture of this vaccine.

The vial stopper does not contain latex.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Influenza illness and its complications follow infection with influenza viruses. Global surveillance of influenza identifies yearly antigenic variants. For example, since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation. Specific levels of HI antibody titer post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza illness but the antibody titers have been used as a measure of vaccine activity. In some human challenge studies, antibody titers of ≥1:40 have been associated with protection from influenza illness in up to 50% of subjects.[1,2] Antibody against one influenza virus type or subtype confers little or no protection

against another virus. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virological basis for seasonal epidemics and the reason for the usual change of one or more new strains in each year's influenza vaccine. Therefore, inactivated influenza vaccines are standardized to contain the hemagglutinins of strains (i.e., typically 2 type A and 1 type B), representing the influenza viruses likely to circulate in the United States in the upcoming winter.

Annual revaccination with the current vaccine is recommended because immunity declines during the year after vaccination, and because circulating strains of influenza virus change from year to year.[3]

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

FLULAVAL has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

## 14 CLINICAL STUDIES

### 14.1 Efficacy Against Culture-Confirmed Influenza

The efficacy of FLULAVAL was evaluated in a randomized, double-blind, placebo-controlled study conducted in the United States during the 2005-2006 and 2006-2007 influenza seasons (Study 3). Efficacy of FLULAVAL was defined as the prevention of culture-confirmed influenza A and/or B cases, for vaccine antigenically matched strains, compared with placebo. Healthy subjects 18 to 49 years of age were randomized (1:1); a total of 3,783 subjects received FLULAVAL and 3,828 subjects received placebo *[see Adverse Reactions (6.1)]*. Subjects were monitored for influenza-like illnesses (ILI) starting 2 weeks post-vaccination and for duration of approximately 7 months thereafter. Culture-confirmed influenza was assessed by active and passive surveillance of ILI. Influenza-like illness was defined as illness sufficiently severe to limit daily activity and including cough, and at least one of the following: Fever >99.9°F, nasal congestion or runny nose, sore throat, myalgia or arthralgia, headache, feverishness or chills. After an episode of ILI, nose and throat swab samples were collected for analysis; attack rates and vaccine efficacy were calculated using the per protocol cohort (Table 2).

**Table 2. Vaccine Efficacy Against Culture-Confirmed Influenza (Per Protocol Cohort)**

| | | | Attack Rates (n/N) | Vaccine Efficacy | |
|---|---|---|---|---|---|
| | N[a] | n[b] | % | % | 97.5% CI Lower Limit |
| **Antigenically Matched Strains** | | | | | |
| FLULAVAL | 3,714 | 23 | 0.6 | 46.3 | 9.8[c] |
| Placebo | 3,768 | 45 | 1.2 | – | – |
| **All Culture-Confirmed Influenza (Matched, Unmatched, and Untyped)** | | | | | |
| FLULAVAL | 3,714 | 30 | 0.8 | 49.3 | 20.3 |
| Placebo | 3,768 | 60 | 1.6 | – | – |

CI = Confidence Interval.

[a] Per Protocol Cohort for efficacy included subjects with no protocol deviations considered to compromise efficacy data.

[b] Number of influenza cases.

[c] Lower limit of the 97.5% CI for vaccine efficacy against influenza due to antigenically matched strains was less than the pre-defined success criterion of ≥35%.

## 14.2 Immunological Evaluation

Study 1 (Immunogenicity): In a randomized, active-controlled trial of FLULAVAL, immune responses, specifically HI antibody titers to each virus strain in the vaccine, were evaluated in sera obtained 21 days after administration of FLULAVAL.

A 1,000-subject randomized, blinded, and controlled US study was performed in 18- to 64-year-old healthy adults. A total of 721 subjects received FLULAVAL, and 279 received a US-licensed trivalent, inactivated influenza virus vaccine, FLUZONE (manufactured by Sanofi Pasteur SA), intramuscularly; 959 subjects had complete serological data and no major protocol deviations *[see Adverse Reactions (6.1)]*.

Analyses of immunogenicity (Table 3) were performed for each hemagglutinin (HA) antigen contained in the vaccine: 1) assessment of the lower bounds of 2-sided 95% confidence intervals for the proportion of subjects with HI antibody titers of ≥1:40 after vaccination, and 2) assessment of the lower bounds of 2-sided 95% confidence intervals for rates of seroconversion (defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer ≥1:10, or an increase in titer from <1:10 to ≥1:40). The pre-specified success criteria for HI titer ≥1:40 was 70% and for seroconversion rate was 40%. The lower limit of the 2-sided 95% CI for the percentage of subjects who achieved an HI titer of ≥1:40 exceeded the pre-defined criteria for the A strains. The lower limit of the 2-sided 95% CI for the percentage of subjects who achieved seroconversion exceeded the pre-defined criteria for all 3 strains.

**Table 3. Serum Hemagglutination-Inhibiting (HI) Antibody Responses to FLULAVAL[a] (Per Protocol Cohort[b])**

| | FLULAVAL N = 692 % of Subjects (95% CI) | |
|---|---|---|
| **HI titers ≥1:40 against:** | **Pre-vaccination** | **Post-vaccination** |
| A/New Caledonia/20/99 (H1N1) | 24.6 | 96.5 (94.9, 97.8) |
| A/Wyoming/03/03 (H3N2) | 58.7 | 98.7 (97.6, 99.4) |
| B/Jiangsu/10/03 | 5.4 | 62.9 (59.1, 66.5) |
| **Seroconversion[c] to:** | | |
| A/New Caledonia/20/99 (H1N1) | 85.6 (82.7, 88.1) | |
| A/Wyoming/03/03 (H3N2) | 79.3 (76.1, 82.3) | |
| B/Jiangsu/10/03 | 58.4 (54.6, 62.1) | |

CI = Confidence Interval.

[a] Results obtained following vaccination with FLULAVAL manufactured for the 2004–2005 season.

[b] Per Protocol Cohort for immunogenicity included subjects with complete pre- and post-dose HI titer data and no major protocol deviations.

[c] Seroconversion defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer ≥1:10, or an increase in titer from <1:10 to ≥1:40.

Study 2 (Immunogenicity Non-Inferiority): In a randomized, double-blind, active-controlled US study, immunological non-inferiority of FLULAVAL was compared with a US-licensed trivalent, inactivated influenza virus vaccine, FLUZONE, manufactured by Sanofi Pasteur SA. A total of 1,225 adults ≥50 years of age in stable health were randomized to receive FLULAVAL or the comparator vaccine intramuscularly *[see Adverse Reactions (6.1)]*. Immune responses, specifically HI antibody titers to each virus strain in the vaccine, were evaluated in sera obtained 21 days after administration of FLULAVAL or the comparator vaccine.

Analyses of immunogenicity were performed for each HA antigen contained in the vaccines: 1) assessment of the lower bounds of 2-sided 95% confidence intervals for the geometric mean antibody titer (GMT) ratio (FLULAVAL/comparator), and 2) assessment of the lower bounds of 2-sided 95% confidence intervals for seroconversion rates (defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer ≥1:10, or an increase in titer from <1:10 to ≥1:40). Non-inferiority of FLULAVAL to the comparator vaccine was established for all 6 co-primary endpoints (Table 4). Within each age stratum, immunogenicity results were similar between the groups.

**Table 4. Serum Hemagglutination-Inhibiting (HI) Antibody Responses to FLULAVAL Versus Comparator Influenza Vaccine[a] (Per Protocol Cohort[b])**

| | FLULAVAL N = 592 | Active Comparator[c] N = 595 | |
|---|---|---|---|
| **Day 21 Post-vaccination GMTs Against:** | **GMT (95% CI)** | **GMT (95% CI)** | **GMT Ratio[d] (95% CI)** |
| A/New Caledonia/20/99 (H1N1) | 113.4 (104.7, 122.8) | 110.2 (101.8, 119.3) | 1.03 (0.92, 1.15) |
| A/New York/55/04 (H3N2) | 223.9 (199.5, 251.3) | 214.6 (191.3, 240.7) | 1.04 (0.89, 1.23) |
| B/Jiangsu/10/03 | 82.3 (74.7, 90.6) | 97.1 (88.2, 106.8) | 0.85 (0.74, 0.97) |
| **Seroconversion[e] to:** | **% of Subjects (95% CI)** | **% of Subjects (95% CI)** | **Difference in Seroconversion Rates[f] (95% CI)** |
| A/New Caledonia/20/99 (H1N1) | 34 (30.0, 37.6) | 32 (28.3, 35.9) | 2 (-3.7, 7.0) |
| A/New York/55/04 (H3N2) | 83 (80.3, 86.3) | 82 (78.4, 84.6) | 1 (-2.6, 6.1) |
| B/Jiangsu/10/03 | 53 (49.0, 57.1) | 56 (51.6, 59.6) | -3 (-8.3, 3.1) |

CI = Confidence Interval; GMT = geometric mean antibody titer.

[a] Results obtained following vaccination with influenza vaccines manufactured for the 2005-2006 season.

[b] Per Protocol Cohort for immunogenicity included subjects with complete pre- and post-dose HI titer data and no major protocol deviations.

[c] US-licensed trivalent, inactivated influenza virus vaccine (manufactured by Sanofi Pasteur SA).

[d] FLULAVAL met non-inferiority criteria based on GMTs (lower limit of 2-sided 95% CI for GMT ratio [FLULAVAL/comparator vaccine] ≥0.67).

[e] Seroconversion defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer ≥1:10, or an increase in titer from <1:10 to ≥1:40.

[f] FLULAVAL met non-inferiority criteria based on seroconversion rates (lower limit of 2-sided 95% CI for difference of FLULAVAL minus the comparator vaccine ≥-10%).

## 15 REFERENCES

1. Hannoun C, Megas F, Piercy J. Immunogenicity and protective efficacy of influenza vaccination. *Virus Res* 2004;103:133-138.

2. Hobson D, Curry RL, Beare AS, et al. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. *J Hyg Camb* 1972;70:767-777.
3. Centers for Disease Control and Prevention. Prevention and control of influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2010;59(RR-8):1-62.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

FLULAVAL is supplied in a 5-mL multi-dose vial containing ten 0.5-mL doses. Once entered, the multi-dose vial should be discarded after 28 days.

Store refrigerated between 2º and 8ºC (36º and 46ºF). Do not freeze. Discard if the vaccine has been frozen. Store in the original package to protect from light.

NDC 19515-888-07 (package of 1 vial containing 10 doses)

## 17 PATIENT COUNSELING INFORMATION

- Inform the vaccine recipient or guardian of the potential benefits and risks of immunization with FLULAVAL.
- Emphasize, when educating vaccine recipients or guardians regarding potential side effects, that (1) FLULAVAL contains non-infectious killed viruses and cannot cause influenza and (2) FLULAVAL is intended to provide protection against illness due to influenza viruses only, and cannot provide protection against all respiratory illness.
- Instruct the vaccine recipient or guardian to report any adverse events to their healthcare provider.
- Inform the vaccine recipient or guardian that safety and efficacy have not been established in pregnant women. Register women who receive FLULAVAL while pregnant in the pregnancy registry by calling 1-888-452-9622.
- Provide the vaccine recipient or guardian Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).
- Instruct the vaccine recipient or guardian that annual revaccination is recommended.




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Quebec City, QC, Canada, US License 1739
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