FLULAVAL (Influenza Virus Vaccine) Suspension for Intramuscular Injection 2010-2011 Formula Initial U.S. Approval: 2006

INDICATIONS AND USAGE
- FLULAVAL is an inactivated influenza virus vaccine indicated for active immunization of adults 18 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. (1)
- This indication is based on immune response elicited by FLULAVAL, and there have been no controlled trials 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 systemic hypersensitivity reactions to egg proteins (a vaccine component) or a life threatening-reaction to previous influenza vaccination. (4)

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
- Most common (≥10%) local adverse events were pain, redness, and/or swelling at the injection site. (6.1)
- Most common (≥10%) systemic adverse events were headache, fatigue, myalgia, low grade fever, and malaise. (6.1)

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

Drug Interactions
- Do not mix with any other vaccine in the same syringe or vial. (7.1)
- Immunosuppressive therapies may reduce immune responses to FLULAVAL. (7.2)

Use in Specific Populations
- Safety and effectiveness of FLULAVAL have not been established in pregnant women, nursing mothers, and children. (8.1, 8.3, 8.4)
- Geriatric Use: Antibody responses were lower in geriatric subjects than in younger subjects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: May 2010
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
FLULAVAL® is indicated for active immunization of adults (18 years of age and older) against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

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

2 DOSAGE AND ADMINISTRATION

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.

The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk. A needle length of ≥1 inch is preferred because needles <1 inch might be of insufficient length to penetrate muscle tissue in certain adults.

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.

4 CONTRAINDICATIONS
Do not administer FLULAVAL to anyone with known systemic hypersensitivity reactions to egg proteins (a vaccine component) or a life-threatening reaction to previous administration of any influenza vaccination [see Description (11)].
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 patient’s immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions. 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 event 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 clinical trials, the most common (≥10%) local and systemic adverse events were pain, redness, and/or swelling at the injection site, headache, fatigue, myalgia, low grade fever, and malaise.

Safety information for FLULAVAL was collected in 2 randomized, controlled clinical trials, one in the United States (IDB707-105) and the second in Canada (SPD707-104). The safety population from these trials includes 1,049 adults 18 years of age and older vaccinated with products representative of the licensed formulation of FLULAVAL. The US study included subjects 18 to 64 years of age who were randomized to receive FLULAVAL (N = 721) or a US-licensed trivalent, inactivated influenza virus vaccine (FLUZONE) (N = 279). The Canadian study compared 4 vaccine groups: FLULAVAL, a similar investigational formulation of FLULAVAL with reduced thimerosal, and 2 Canadian-licensed trivalent influenza vaccines.

Among recipients of FLULAVAL, 56.6% were women; 92.4% of subjects were white,
6.5% black, 2.7% Native American, and 1.0% Asian. In the US study, 74.8% of the recipients of FLULAVAL were Hispanic/Latino. The mean age of subjects in the US study was 38 years (range 18-64 years) and 19% of subjects were 50 to 64 years of age. In the Canadian study, the mean age was 63 years (range 50-92 years), and 46.6% were 65 years of age and older.

A series of symptoms and/or findings were specifically solicited by a diary/memory aid used by subjects for at least the day of vaccination and 3 days post-treatment (Table 1). Subjects were actively queried about changes in their health status through 42 days post-vaccination in the US trial, and six months post-vaccination in the Canadian study. In addition, spontaneous reports of adverse events were also collected (Table 2).

### Table 1. Solicited Adverse Events in the First 4 Days After Administration of FLULAVAL or Comparator Influenza Vaccine

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>US Trial Adults 18 to 64 years of age (80% &lt;50 years of age)</th>
<th>Comparator Influenza Vaccinea</th>
<th>Canadian Trial Adults 50 years of age and older</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FLULAVAL (N = 721) %</td>
<td>Comparator Influenza Vaccineb (N = 279) %</td>
<td>FLULAVALb (N = 328) %</td>
</tr>
<tr>
<td>Local</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>24</td>
<td>31</td>
<td>21</td>
</tr>
<tr>
<td>Redness</td>
<td>11</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Swelling</td>
<td>10</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Systemic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>18</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Myalgia</td>
<td>13</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Feverc</td>
<td>11</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Malaise</td>
<td>10</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Sore throat</td>
<td>9</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Reddened eyes</td>
<td>6</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Cough</td>
<td>6</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Chills</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Chest tightness</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Facial swelling</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Results >1% reported to nearest whole percent; results >0 but ≤1 reported as 1%.

- **a** US-licensed trivalent, inactivated influenza virus vaccine (FLUZONE).
- **b** Includes subjects who received FLULAVAL and a similar investigational formulation of FLULAVAL with reduced thimerosal.
- **c** Fever defined as ≥37.5°C in the US study, and ≥38.0°C in the Canadian study.
Local adverse events occurred with similar frequency in the 2 trials. In the US study, the only significant difference between FLULAVAL and a US-licensed trivalent, inactivated influenza virus vaccine was an increased frequency of chills in subjects receiving FLULAVAL.

Table 2 summarizes the most common adverse events in the 2 clinical trials; adverse events were reported, either spontaneously or in response to queries about changes in health status. The most common events were headache and cough in both studies. These, as well as throat pain, were the only adverse events reported by >1% of subjects in the US trial. The Canadian trial featured a longer safety follow-up (6 months vs. 42 days) and enrolled a population exclusively 50 years of age and older. Therefore, spontaneous adverse event reports were more frequent in this trial. As indicated in Table 2, upper respiratory infection, arthralgia, myalgia, nasopharyngitis, back pain, injection site erythema, diarrhea, fatigue, nausea, and nasal congestion were each reported by ≥5% of the recipients of FLULAVAL in the Canadian study.

Table 2. Adverse Events Reported Spontaneously\(^a\) by ≥5% of Subjects in Either Clinical Trial of FLULAVAL

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>US Trial (safety follow-up 42 days)</th>
<th>Canadian Trial (safety follow-up 6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FLULAVAL ( N = 721 ) %</td>
<td>Comparator Influenza Vaccine(^b) ( N = 279 ) %</td>
</tr>
<tr>
<td>Headache</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Cough</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Back pain</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Results >1% reported to nearest whole percent; results >0 but ≤1 reported as 1%.

\(^a\) Adverse events in this table were reported spontaneously or in response to queries about

\(^b\) Trivalent, inactivated influenza virus vaccine licensed in the US.

\(^c\) FLULAVAL licensed in Canada.
changes in health status.

b US-licensed trivalent, inactivated influenza virus vaccine (FLUZONE).
c Includes subjects who received FLULAVAL and a similar investigational formulation of FLULAVAL with reduced thimerosal.

6.2 Postmarketing Experience

The following additional 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:** Conjunctivitis, eye pain, photophobia.

**Gastrointestinal Disorders:** Dysphagia, vomiting.

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

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

**Infections and Infestations:** Pharyngitis, rhinitis, laryngitis, cellulitis.

**Musculoskeletal and Connective Tissue Disorders:** Muscle weakness, back pain, 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, periorbital edema, 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.

7.3 Warfarin, Theophylline, and Phenytoin

Although it has been reported that influenza vaccination may inhibit the clearance of warfarin, theophylline, and phenytoin, controlled studies have yielded inconsistent results regarding pharmacokinetic interactions between influenza vaccine and these medications. Nevertheless, clinicians should consider the potential for an interaction when FLULAVAL is administered to persons receiving these drugs.

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.
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 the 2 clinical trials, there were 157 subjects who were ≥65 years of age and received
FLULAVAL; 21 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. 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-
nerion, 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 2010-2011 influenza season and is formulated to contain 45 mcg
hemagglutinin per 0.5-mL dose in the recommended ratio of 15 mcg HA of each of the following
(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
In 2 randomized, active-controlled trials of FLULAVAL, the immune responses, specifically HI antibody titers to each virus strain in the vaccine, were evaluated in sera obtained 21 days after administration of FLULAVAL. No controlled trials demonstrating a decrease in influenza disease after vaccination with FLULAVAL have been performed.

A 1,000-subject randomized, blinded, and controlled study was performed in the United States 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); 959 subjects had complete serological data and no major protocol deviations. Among recipients of FLULAVAL, 57.4% were women. The mean age of recipients of FLULAVAL was 37.9 years; 80.4% were 18 to 49 years of age and 19.6% were 50 to 64 years of age.

A second, randomized, blinded, and controlled study which enrolled 658 subjects 50 years of age and older (stratified by age <65 and ≥65 years) was conducted in Canada. This study included elderly persons with medically controlled chronic high-risk diagnoses who were clinically stable. This study compared 4 vaccine groups: FLULAVAL, a similar investigational formulation of FLULAVAL with reduced thimerosal, and 2 Canadian-licensed trivalent influenza vaccines. Results from the 2 groups that received FLULAVAL were submitted in support of the US licensure of FLULAVAL. Among these 2 groups, 54.9% of subjects were women. The mean age of recipients of FLULAVAL was 63 years; 53.4% were 50 to 64 years of age and 46.6% were 65 years of age and older.

For both studies, analysis of the following co-primary endpoints (Table 3) were performed for each 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 $\geq 1:10$, or an increase in titer from $<1:10$ to $\geq 1:40$). The pre-specified targets for the 2 endpoints varied by study because of age of subjects enrolled. The pre-specified target for endpoint 1) was 70% in the US study and 60% in the Canadian study. For endpoint 2) the pre-specified target was 40% in the US study and 30% in the Canadian study. For the Canadian study, the primary endpoints, as originally designed, were descriptive comparisons of immune response; therefore, a post-hoc analysis of the endpoints, as described above, was performed.

Table 3. Serum Hemagglutination-Inhibiting (HI) Antibody Responses to FLULAVAL in 2 Clinical Trials$^a$ (Per Protocol Cohort)$^b$

<table>
<thead>
<tr>
<th>US Trial in Adults 18 to 64 years of age</th>
<th>% of Subjects (lower bound of 2-sided 95% confidence interval)$^c$</th>
<th>FLULAVAL N = 692</th>
<th>Primary endpoint met post-vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>HI titers $\geq 1:40$ against:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/New Caledonia/20/99 (H1N1)</td>
<td>Pre-vaccination 24.6 Post-vaccination 96.5 (94.9)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>A/Wyoming/03/03 (H3N2)</td>
<td>58.7 98.7 (97.6)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>B/Jiangsu/10/03</td>
<td>5.4 62.9 (59.1)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Seroconversion$^d$ to:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/New Caledonia/20/99 (H1N1)</td>
<td>85.6 (82.7)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>A/Wyoming/03/03 (H3N2)</td>
<td>79.3 (76.1)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>B/Jiangsu/10/03</td>
<td>58.4 (54.6)</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Canadian Trial in Adults $\geq 50$ years of age</th>
<th>% of Subjects (lower bound of 2-sided 95% confidence interval)$^c$</th>
<th>FLULAVAL$^e$ N = 324</th>
<th>Primary endpoint met post-vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>HI titers $\geq 1:40$ against:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/New Caledonia/20/99 (H1N1)</td>
<td>Pre-vaccination 39.5 Post-vaccination 86.4 (82.2)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>A/Wyoming/03/03 (H3N2)</td>
<td>67.9 99.1 (97.3)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>B/Jiangsu/10/03</td>
<td>10.2 57.1 (51.5)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Seroconversion$^d$ to:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/New Caledonia/20/99 (H1N1)</td>
<td>44.8 (39.3)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>A/Wyoming/03/03 (H3N2)</td>
<td>69.1 (63.8)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>B/Jiangsu/10/03</td>
<td>49.1 (43.5)</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ 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.

$^c$ Lower bounds were calculated using Clopper-Pearson method.

$^d$ Seroconversion = a 4-fold increase post-vaccination in HI antibody titer from pre-vaccination titer $\geq 1:10$, or an increase in titer from $<1:10$ to $\geq 1:40$.

$^e$ Includes subjects who received FLULAVAL and a similar investigational formulation of FLULAVAL.
with reduced thimerosal.

Across both studies, serum HI antibody responses to FLULAVAL met the pre-specified seroconversion criteria for all 3 virus strains, and also the pre-specified criterion for the proportion of subjects with HI titers \( \geq 1:40 \) for both influenza A viruses. In both trials, both FLULAVAL and the comparator vaccine did not meet the pre-specified criterion for the proportion of subjects with HI titers \( \geq 1:40 \) for the influenza B virus. The clinical relevance of this finding on vaccine-induced protection against illness caused by influenza type B strains is unknown.

15 REFERENCES

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 19515-887-07 (package of 1 vial containing 10 doses)

17 PATIENT COUNSELING INFORMATION
The vaccine recipient or guardian should be:
- informed of the potential benefits and risks of immunization with FLULAVAL.
- educated regarding potential side effects, emphasizing 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.
- instructed to report any adverse events to their healthcare provider.
- given the 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).
- instructed that annual revaccination is recommended.
FLULAVAL is a registered trademark of ID Biomedical Corporation of Quebec. FLUZONE is a trademark of Sanofi Pasteur Limited.

Manufactured by **ID Biomedical Corporation of Quebec**
Quebec City, QC, Canada, US License 1739
Distributed by **GlaxoSmithKline**
Research Triangle Park, NC 27709

©2010, GlaxoSmithKline. All rights reserved.

May 2010
FLV:6PI