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 Vaccine)
Suspension for Intramuscular Injection
2015-2016 Formula
Initial U.S. Approval: 2006

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

FLULAVAL is a vaccine indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B virus contained in the vaccine. FLULAVAL is approved for use in persons 3 years of age and older. (1)

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

For intramuscular injection only. (2)

Age	Vaccination Status	Dose and Schedule
Aged 3 through 8 years	Not previously vaccinated with influenza vaccine	Two doses (0.5-mL each) at least 4 weeks apart (2.1)
	Vaccinated with influenza vaccine in a previous season	One or two doses[a] (0.5-mL each) (2.1)
Aged 9 years and older	Not applicable	One 0.5-mL dose (2.1)

[a] One dose or two doses (0.5-mL each) depending on vaccination history as per the annual Advisory Committee on Immunization Practices (ACIP) recommendation on prevention and control of influenza with vaccines. If two doses, administer each 0.5-mL dose at least 4 weeks apart. (2.1)

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

Suspension for injection in 0.5-mL single-dose prefilled syringes and 5-mL multi-dose vials containing 10 doses (each dose is 0.5 mL). (3)

----------CONTRAINDICATIONS----------

History of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or following a previous dose of any influenza vaccine. (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)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including FLULAVAL. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.2)

---------- ADVERSE REACTIONS ----------

- In adults, the most common (≥10%) solicited local adverse reactions were pain (51%), redness (13%), and/or swelling (11%); the most common solicited systemic adverse events were fatigue (20%), headache (18%), and muscle aches/arthralgia (18%). (6.1)
- In children aged 3 through 17 years, the most common (≥10%) solicited local adverse reaction was pain (56%). (6.1)
- In children aged 3 through 4 years, the most common (≥10%) solicited systemic adverse events were irritability (25%), drowsiness (19%), and loss of appetite (16%). (6.1)
- In children aged 5 through 17 years, the most common (≥10%) solicited systemic adverse events were muscle aches (24%), headache (17%), and fatigue (17%). (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.

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

- Safety and effectiveness of FLULAVAL have not been established in pregnant women or nursing mothers. (8.1, 8.3)
- 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 who received FLULAVAL than in younger subjects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: XX/201X

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FLULAVAL® is indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B virus contained in the vaccine. FLULAVAL is approved for use in persons 3 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Dosage and Schedule

The dose and schedule for FLULAVAL are presented in Table 1.

Table 1. FLULAVAL: Dosing

Age	Vaccination Status	Dose and Schedule
Aged 3 through 8 years	Not previously vaccinated with influenza vaccine	Two doses (0.5-mL each) at least 4 weeks apart
	Vaccinated with influenza vaccine in a previous season	One or two doses[a] (0.5-mL each)
Aged 9 years and older	Not applicable	One 0.5-mL dose

[a] One dose or two doses (0.5-mL each) depending on vaccination history as per the annual Advisory Committee on Immunization Practices (ACIP) recommendation on prevention and control of influenza with vaccines. If two doses, administer each 0.5-mL dose at least 4 weeks apart.

2.2 Administration Instructions

Shake well before administration. 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.

Attach a sterile needle to the prefilled syringe and administer intramuscularly.

For the multi-dose vial, use a sterile needle and sterile syringe to withdraw the 0.5-mL dose from the multi-dose vial and administer intramuscularly. A sterile syringe with a needle bore no larger than 23 gauge is recommended for administration. It is recommended that small syringes (0.5 mL or 1 mL) be used to minimize any product loss. Use a separate sterile needle and syringe for each dose withdrawn from the multi-dose vial**.**

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.

The preferred site for intramuscular injection is the deltoid muscle of the upper arm. Do not inject in the gluteal area or areas where there may be a major nerve trunk.

Do not administer this product intravenously, intradermally, or subcutaneously.

3 DOSAGE FORMS AND STRENGTHS

FLULAVAL is a suspension for injection available in 0.5-mL prefilled TIP-LOK® syringes and 5-mL multi-dose vials containing 10 doses (each dose is 0.5 mL).

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

If Guillain-Barré syndrome (GBS) 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.

The 1976 swine influenza vaccine was associated with an elevated risk of GBS. Evidence for a causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than one additional case/one million persons vaccinated.

5.2 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines, including FLULAVAL. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

5.3 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. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of FLULAVAL.

5.4 Altered Immunocompetence

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

5.5 Limitations of Vaccine Effectiveness

Vaccination with FLULAVAL may not protect all susceptible individuals.

5.6 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.

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 with rates in the clinical trials of another vaccine, and may not reflect the rates observed in practice. There is the possibility that broad use of FLULAVAL could reveal adverse reactions not observed in clinical trials.

In adults who received FLULAVAL, the most common (≥10%) solicited local adverse reactions were pain (51%), redness (13%), and swelling (11%); the most common (≥10%) solicited systemic adverse events were fatigue (20%), headache (18%), and muscle aches/arthralgia (18%).

In children aged 3 through 17 years who received FLULAVAL, the most common (≥10%) solicited local adverse reaction was pain (56%). In children aged 3 through 4 years, the most common (≥10%) solicited systemic adverse events were irritability (25%), drowsiness (19%), and loss of appetite (16%). In children aged 5 through 17 years, the most common (≥10%) systemic adverse events were muscle aches (24%), headache (17%), and fatigue (17%).

FLULAVAL in Adults

Safety data was obtained from 3 randomized, controlled trials, one of which was a placebo-controlled efficacy trial. 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 vaccine, manufactured by Sanofi Pasteur SA (894 subjects in the safety analysis), or placebo (3,828 subjects in the safety analysis), intramuscularly. In these trials, solicited events were collected for 4 days (i.e., 30 minutes post-vaccination through the next 3 days). Unsolicited adverse events that occurred within 22 days of vaccination (Day 0 to 21) were recorded based on spontaneous reports or in response to queries about changes in health status.

Trial 1 (Immunogenicity): Safety information was collected in a randomized, controlled US trial. This trial included 1,000 adults aged 18 through 64 years who were randomized to receive FLULAVAL (N = 721) or a US-licensed trivalent, inactivated influenza 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 aged 18 through 49 years and 20% were aged 50 through 64 years.

Trial 2 (Immunogenicity Non-Inferiority): Safety information was collected in a randomized, double-blind, active-controlled US trial. The trial included 1,225 adults aged ≥50 years randomized to receive FLULAVAL (N = 610) or a US-licensed trivalent, inactivated influenza 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 aged 50 through 64 years, 41% were aged 65 through 79 years, and 13% were aged ≥80 years.

Trial 3 (Efficacy): Safety information was collected in a double-blind, placebo-controlled US trial. The trial included 7,658 adults aged 18 through 49 years 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 2.

Table 2. FLULAVAL: Incidence of Solicited Local Adverse Reactions and Systemic Adverse Events within 4 Days[a] of Vaccination in Adults (Total Vaccinated Cohort)

	Percentage of Subjects Reporting Event					
	Trial 1[b] Aged 18 through 64 Years		Trial 2[b] Aged 50 Years and Older		Trial 3[b] Aged 18 through 49 Years	
	FLULAVAL N = 721	Comparator[c] N = 279	FLULAVAL N = 610	Comparator[c] N = 615	FLULAVAL N = 3,783	Placebo N = 3,828
Local Adverse Reactions						
Pain	24	31	25	32	51	14
Redness	11	10	10	11	13	6
Swelling	10	10	7	9	11	3
Systemic Adverse Events						
Headache	18	17	11	12	18	19
Fatigue	17	15	12	13	20	18
Muscle aches[d]	13	16	11	10	18	10
Fever ≥99.5°F (37.5°C)	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

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

[a] 4 days included day of vaccination and the subsequent 3 days.

[b] Trial 1: NCT01389479; Trial 2: NCT00232947; Trial 3: NCT00216242.

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

[d] For Trial 2 and Trial 3, includes muscle aches 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 Trial 1 (16% and 15%, respectively) and in Trial 2 (18% and 21%, respectively). In Trial 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: Trial 1: Cough, headache, and pharyngolaryngeal pain; Trial 2: Diarrhea, headache, and nasopharyngitis; and Trial 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 Trial 1, no SAEs were reported. In Trial 2, 3% of subjects receiving FLULAVAL and 3% of subjects receiving the active comparator reported SAEs. In Trial 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.

FLULAVAL in Children

Trial 4 (Immunogenicity Non-Inferiority): An observer-blind, active-controlled US trial evaluated subjects aged 3 through 17 years who received FLULAVAL (N = 1,055) or FLUZONE (N = 1,061), a US-licensed trivalent, inactivated influenza vaccine, manufactured by Sanofi Pasteur SA. In the overall population, 53% were male; 78% of subjects were white, 12% were black, 2% were Asian, and 8% were of other racial/ethnic groups. The mean age of subjects was 8 years. Children aged 3 through 8 years with no history of influenza vaccination received 2 doses approximately 28 days apart. Children aged 3 through 8 years with a history of influenza vaccination and children aged 9 years and older received one dose. Solicited local adverse reactions and systemic adverse events were collected for 4 days (day of vaccination and the next 3 days) (Table 3).

Table 3. FLULAVAL: Incidence of Solicited Local Adverse Reactions and Systemic Adverse Events within 4 Days[a] of First Vaccination in Children Aged 3 through 17 Years[b] (Total Vaccinated Cohort)

	FLULAVAL %	Active Comparator[c] %
	Aged 3 through 17 Years	
Local Adverse Reactions	**N = 1,042**	**N = 1,026**
Pain	56	53
Redness	4	5
Swelling	4	5
	Aged 3 through 4 Years	
Systemic Adverse Events	**N = 293**	**N = 279**
Irritability	25	27
Drowsiness	19	19
Loss of appetite	16	13
Fever ≥100.4°F (38.0°C)	5	3
	Aged 5 through 17 Years	
Systemic Adverse Events	**N = 750**	**N = 747**
Muscle aches	24	23
Headache	17	15
Fatigue	17	17
Arthralgia	8	10
Shivering	6	5
Fever ≥100.4°F (38.0°C)	5	4

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

[a] 4 days included day of vaccination and the subsequent 3 days.

[b] Trial 4: NCT00980005.

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

In children who received a second dose of FLULAVAL or the comparator vaccine, the incidences of adverse events following the second dose were generally lower than those observed after the first dose.

The incidence of unsolicited adverse events that occurred within 28 days (Day 0 to 27) of any vaccination reported in subjects who received FLULAVAL (N = 1,055) or FLUZONE (N = 1,061) was 40% and 37%, respectively. The unsolicited adverse events that occurred most frequently (≥0.1% of subjects for FLULAVAL) and considered possibly related to vaccination included diarrhea, influenza-like illness, injection site hematoma, injection site rash, injection site warmth, rash, upper abdominal pain, and vomiting. The rates of SAEs were comparable between groups (0.9% and 0.6% for FLULAVAL and the comparator, respectively); 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.

General Disorders and Administration Site Conditions

Chest pain, injection site inflammation, asthenia, injection site rash, abnormal gait, injection site bruising, injection site sterile abscess.

Immune System Disorders

Allergic reactions including anaphylaxis, angioedema.

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, pruritus, sweating.

Vascular Disorders

Flushing, pallor.

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

FLULAVAL should not be mixed with any other vaccine in the same syringe or vial.

There are insufficient data to assess the concomitant administration of FLULAVAL with other vaccines. When concomitant administration of other vaccines is required, the vaccines should be administered at different injection sites.

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 40-fold the human dose (on a mg/kg basis) and showed 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 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/dose/rat (approximately 40-fold higher than 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 children younger than 3 years have not been established.

Safety and immunogenicity of FLULAVAL in children aged 3 through 17 years have been evaluated *[see Adverse Reactions (6.1), Clinical Studies (14)]*.

8.5 Geriatric Use

In clinical trials, there were 330 subjects aged 65 years and older who received FLULAVAL; 142 of these subjects were aged 75 years and older. Hemagglutination inhibition 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 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 viruses 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, opalescent, translucent to off-white 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 2015-2016 influenza season and is formulated to contain 45 micrograms (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-179A (H1N1), A/Switzerland/9715293/2013 NIB-88 (H3N2), and B/Phuket/3073/2013.

The prefilled syringe is formulated without preservatives and does not contain thimerosal. Each 0.5-mL dose from the multi-dose vial contains 50 mcg thimerosal (<25 mcg mercury); thimerosal, a mercury derivative, is added as a preservative.

Each 0.5-mL dose of either presentation may also contain residual amounts of ovalbumin (≤0.3 mcg), formaldehyde (≤25 mcg), sodium deoxycholate (≤50 mcg), α-tocopheryl hydrogen

succinate (≤240 mcg), and polysorbate 80 (≤665 mcg) from the manufacturing process. Antibiotics are not used in the manufacture of this vaccine.

The tip caps and plungers of the prefilled syringes are not made with natural rubber latex. The vial stoppers are not made with natural rubber 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. Since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation.

Specific levels of hemagglutination inhibition (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 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. Vaccination of female rats with FLULAVAL, at doses shown to be immunogenic in the rat, had no effect on fertility.

14 CLINICAL STUDIES

The effectiveness of FLULAVAL was demonstrated based on clinical endpoint efficacy data for FLULAVAL QUADRIVALENT (Influenza Vaccine), clinical endpoint efficacy data for FLULAVAL, and on an evaluation of serum HI antibody responses to FLULAVAL. FLULAVAL QUADRIVALENT, an inactivated influenza vaccine that contains the hemagglutinins of two influenza A subtype viruses and two influenza type B viruses, is manufactured according to the same process as FLULAVAL.

14.1 Efficacy against Influenza

Efficacy Trial in Children

The efficacy of FLULAVAL QUADRIVALENT was evaluated in Trial 5, a randomized, observer-blind, non-influenza vaccine-controlled trial conducted in 3 countries in Asia, 3 in Latin America, and 2 in the Middle East/Europe during the 2010-2011 influenza season. Healthy subjects aged 3 through 8 years were randomized (1:1) to receive FLULAVAL QUADRIVALENT (N = 2,584), containing A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/4/2006 (Yamagata lineage) influenza strains, or HAVRIX® (Hepatitis A Vaccine) (N = 2,584), as a control vaccine. Children with no history of influenza vaccination received 2 doses of FLULAVAL QUADRIVALENT or HAVRIX approximately 28 days apart. Children with a history of influenza vaccination received one dose of FLULAVAL QUADRIVALENT or HAVRIX. In the overall population, 52% were male; 60% were Asian, 5% were white, and 35% were of other racial/ethnic groups. The mean age of subjects was 5 years.

Efficacy of FLULAVAL QUADRIVALENT was assessed for the prevention of reverse transcriptase polymerase chain reaction (RT-PCR)-positive influenza A and/or B disease presenting as influenza-like illness (ILI). ILI was defined as a temperature ≥100°F in the presence of at least one of the following symptoms on the same day: cough, sore throat, runny nose, or nasal congestion. Subjects with ILI (monitored by passive and active surveillance for approximately 6 months) had nasal and throat swabs collected and tested for influenza A and/or B by RT-PCR. All RT-PCR-positive specimens were further tested in cell culture. Vaccine efficacy was calculated based on the ATP cohort for efficacy (Table 4).

Table 4. FLULAVAL QUADRIVALENT: Influenza Attack Rates and Vaccine Efficacy against Influenza A and/or B in Children Aged 3 through 8 Years[a] (According-to-Protocol Cohort for Efficacy)

	N[b]	n[c]	Influenza Attack Rate % (n/N)	Vaccine Efficacy % (CI)
All RT-PCR-positive Influenza				
FLULAVAL QUADRIVALENT	2,379	58	2.4	55.4[d] (95% CI: 39.1, 67.3)
HAVRIX[e]	2,398	128	5.3	–
All Culture-confirmed Influenza[f]				
FLULAVAL QUADRIVALENT	2,379	50	2.1	55.9 (97.5% CI: 35.4, 69.9)
HAVRIX[e]	2,398	112	4.7	–
Antigenically Matched Culture-confirmed Influenza				
FLULAVAL QUADRIVALENT	2,379	31	1.3	45.1[g] (97.5% CI: 9.3, 66.8)
HAVRIX[e]	2,398	56	2.3	–

CI = Confidence Interval; RT-PCR = Reverse transcriptase polymerase chain reaction.

[a] Trial 5: NCT01218308.

[b] According-to-protocol cohort for efficacy included subjects who met all eligibility criteria, were successfully contacted at least once post-vaccination, and complied with the protocol-specified efficacy criteria.

[c] Number of influenza cases.

[d] Vaccine efficacy for FLULAVAL QUADRIVALENT met the pre-defined criterion of >30% for the lower limit of the 2-sided 95% CI.

[e] Hepatitis A Vaccine used as a control vaccine.

[f] Of 162 culture-confirmed influenza cases, 108 (67%) were antigenically typed (87 matched; 21 unmatched); 54 (33%) could not be antigenically typed [but were typed by RT-PCR and nucleic acid sequence analysis: 5 cases A (H1N1) (5 with HAVRIX), 47 cases A (H3N2) (10 with FLULAVAL QUADRIVALENT; 37 with HAVRIX), and 2 cases B Victoria (2 with HAVRIX)].

[g] Since only 67% of cases could be typed, the clinical significance of this result is unknown.

In an exploratory analysis by age, vaccine efficacy against RT-PCR-positive influenza A and/or B disease presenting as ILI was evaluated in subjects aged 3 through 4 years and 5 through 8 years; vaccine efficacy was 35.3% (95% CI: -1.3, 58.6) and 67.7% (95% CI: 49.7, 79.2),

respectively. As the trial lacked statistical power to evaluate efficacy within age subgroups, the clinical significance of these results is unknown.

As a secondary objective in the trial, subjects with RT-PCR-positive influenza A and/or B were prospectively classified based on the presence of adverse outcomes that have been associated with influenza infection (defined as fever >102.2°F/39.0°C, physician-verified shortness of breath, pneumonia, wheezing, bronchitis, bronchiolitis, pulmonary congestion, croup and/or acute otitis media, and/or physician-diagnosed serious extra-pulmonary complications, including myositis, encephalitis, seizure and/or myocarditis).

The risk reduction of fever >102.2°F/39.0°C associated with RT-PCR-positive influenza was 71.0% (95% CI: 44.8, 84.8) based on the ATP cohort for efficacy [FLULAVAL QUADRIVALENT (n = 12/2,379); HAVRIX (n = 41/2,398)]. The other pre-specified adverse outcomes had too few cases to calculate a risk reduction. The incidence of these adverse outcomes is presented in Table 5.

Table 5. FLULAVAL QUADRIVALENT: Incidence of Adverse Outcomes Associated with RT-PCR-positive Influenza in Children Aged 3 through 8 Years[a] (Total Vaccinated Cohort)[b]

	FLULAVAL QUADRIVALENT N = 2,584			HAVRIX[c] N = 2,584		
Adverse Outcome[d]	**Number of Events**	**Number of Subjects[e]**	**%**	**Number of Events**	**Number of Subjects[e]**	**%**
Fever >102.2°F/39.0°C	16[f]	15	0.6	51[f]	50	1.9
Shortness of breath	0	0	0	5	5	0.2
Pneumonia	0	0	0	3	3	0.1
Wheezing	1	1	0	1	1	0
Bronchitis	1	1	0	1	1	0
Pulmonary congestion	0	0	0	1	1	0
Acute otitis media	0	0	0	1	1	0
Bronchiolitis	0	0	0	0	0	0
Croup	0	0	0	0	0	0
Encephalitis	0	0	0	0	0	0
Myocarditis	0	0	0	0	0	0
Myositis	0	0	0	0	0	0
Seizure	0	0	0	0	0	0

[a] Trial 5: NCT01218308.

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

[c] Hepatitis A Vaccine used as a control vaccine.

[d] In subjects who presented with more than one adverse outcome, each outcome was counted in the respective category.

[e] Number of subjects presenting with at least one event in each group.

[f] One subject in each group had sequential influenza due to influenza type A and type B viruses.

Efficacy Trial in Adults

The efficacy of FLULAVAL was evaluated in a randomized, double-blind, placebo-controlled trial conducted in the United States during the 2005-2006 and 2006-2007 influenza seasons (Trial 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 aged 18 through 49 years 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, muscle aches 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 6). Of note, the 1.2% attack rate in the placebo group for culture-confirmed, antigenically matched strains was lower than expected, contributing to a wide confidence interval for the estimate of vaccine efficacy.

Table 6. FLULAVAL: Influenza Attack Rates and Vaccine Efficacy against Culture-confirmed Influenza in Adults Aged 18 through 49 Years[a] (Per Protocol Cohort)

			Influenza Attack Rates	**Vaccine Efficacy**	
	N[b]	**n[c]**	**% (n/N)**	**%**	**97.5% CI Lower Limit**
Antigenically Matched Strains					
FLULAVAL	3,714	23	0.6	46.3	9.8[d]
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] Trial 3: NCT00216242.

[b] Per Protocol Cohort for efficacy included subjects with no protocol deviations considered to

compromise efficacy data.

[c] Number of influenza cases.

[d] Lower limit of the one-sided 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

Adults

Trial 1 was a randomized, blinded, active-controlled US trial performed in healthy adults aged 18 through 64 years (N = 1,000). A total of 721 subjects received FLULAVAL, and 279 received a US-licensed trivalent, inactivated influenza 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 7) 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 7. Immune Responses to Each Antigen 21 Days after Vaccination with FLULAVAL[a] in Adults Aged 18 through 64 Years (Per Protocol Cohort)[b]

	FLULAVAL N = 692 % of Subjects (95% CI)	
HI titers ≥1:40	**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)	

HI = hemagglutination inhibition; 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 titers from pre-vaccination titer ≥1:10, or an increase in titer from <1:10 to ≥1:40.

Trial 2 (Immunogenicity Non-Inferiority): In a randomized, double-blind, active-controlled US trial, immunological non-inferiority of FLULAVAL was compared with a US-licensed trivalent, inactivated influenza vaccine, FLUZONE, manufactured by Sanofi Pasteur SA. A total of 1,225 adults aged 50 years and older in stable health were randomized to receive FLULAVAL or the comparator vaccine intramuscularly *[see Adverse Reactions (6.1)]*.

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 8). Within each age stratum, immunogenicity results were similar between the groups.

Table 8. Immune Responses to Each Antigen 21 Days after Vaccination with FLULAVAL Versus Comparator Influenza Vaccine in Adults Aged 50 Years and Older[a] (Per Protocol Cohort)[b]

	FLULAVAL N = 592	Active Comparator[c] N = 595	
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)

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

[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 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%).

Children

In Trial 4, the immune response of FLULAVAL (N = 987) was compared to FLUZONE, a

US-licensed trivalent, inactivated influenza vaccine (N = 979), manufactured by Sanofi Pasteur SA, in an observer-blind, randomized trial in children aged 3 through 17 years. The immune responses to each of the antigens contained in FLULAVAL formulated for the 2009-2010 season were evaluated in sera obtained after one or 2 doses of FLULAVAL and were compared to those following the comparator influenza vaccine *[see Adverse Reactions (6.1)]*.

The non-inferiority endpoints were GMTs adjusted for baseline, and the percentage of subjects who achieved seroconversion, defined as at least a 4-fold increase in serum HI titer over baseline to ≥1:40, following vaccination, performed on the According-to-Protocol (ATP) cohort. FLULAVAL was non-inferior to the comparator influenza for all strains based on adjusted GMTs and seroconversion rates (Table 9).

Table 9. Immune Responses to Each Antigen 28 Days after Last Vaccination with FLULAVAL Versus Comparator Influenza Vaccine in Children Aged 3 through 17 Years[a] (According-to-Protocol Cohort for Immunogenicity)[b]

	FLULAVAL	**Active Comparator[c]**	
GMTs Against	**N = 987 (95% CI)**	**N = 979 (95% CI)**	**GMT Ratio[d] (95% CI)**
A/Brisbane (H1N1)	320.9 (298.3, 345.2)	329.4 (306.8, 353.7)	1.03 (0.94, 1.13)
A/Uruguay (H3N2)	414.7 (386.5, 444.9)	451.9 (423.8, 481.8)	1.05 (0.96, 1.13)
B/Brisbane	213.7 (198.5, 230.1)	200.2 (186.1, 215.3)	0.93 (0.85, 1.02)
Seroconversion[e] to:	**N = 987 % (95% CI)**	**N = 978 % (95% CI)**	**Difference in Seroconversion Rate[f] (95% CI)**
A/Brisbane (H1N1)	59.8 (56.6, 62.9)	58.2 (55.0, 61.3)	-1.6 (-5.9, 2.8)
A/Uruguay (H3N2)	68.2 (65.2, 71.1)	66.2 (63.1, 69.1)	-2.0 (-6.1, 2.1)
B/Brisbane	81.1 (78.5, 83.5)	78.6 (75.9, 81.2)	-2.4 (-6.0, 1.1)

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

[a] Results obtained following vaccination with influenza vaccines formulated for the 2009-2010 season.

[b] According-to-protocol cohort for immunogenicity included all evaluable subjects for whom assay results were available after vaccination for at least one trial vaccine antigen.

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

[d] FLULAVAL met non-inferiority criteria based on GMTs (upper limit of 2-sided 95% CI for GMT ratio [comparator vaccine/FLULAVAL] ≤1.5).

[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 (upper limit of 2-sided 95% CI for difference of the comparator vaccine minus FLULAVAL ≤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 available in 0.5-mL single-dose disposable prefilled TIP-LOK syringes (packaged without needles) and in 5-mL multi-dose vials containing 10 doses (0.5-mL each).

NDC 19515-850-41 Syringe in Package of 10: NDC 19515-850-52

NDC 19515-845-01 Multi-Dose Vial (containing 10 doses) in Package of 1: NDC 19515-845-11

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. Once entered, a multi-dose vial should be discarded after 28 days.

17 PATIENT COUNSELING INFORMATION

Provide the following information to the vaccine recipient or guardian:

- Inform of the potential benefits and risks of immunization with FLULAVAL.
- Educate 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.
- Inform 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.

- Give the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 prior to each immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).
- Instruct that annual revaccination is recommended.

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