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
20XX-20XX Formula
Initial U.S. Approval: 2006

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	11/2016
Dosage and Administration (2.1, 2.2)	11/2016

---------- 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 aged 6 months and older. (1)

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

For intramuscular injection only. (2)

Age	Vaccination Status	Dose and Schedule
6 months 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)
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:

- 0.5-mL single-dose prefilled syringes (3)
- 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 who received FLULAVAL, 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 who received FLULAVAL, the most common (≥10%) solicited local adverse reaction was pain (56%). (6.1)
- In children aged 3 through 4 years who received FLULAVAL, 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 who received FLULAVAL, the most common (≥10%) solicited systemic adverse events were muscle aches (24%), headache (17%), and fatigue (17%). (6.1)
- In children aged 6 through 35 months who received FLULAVAL QUADRIVALENT, the most common (≥10%) solicited local adverse reaction was pain (40%); most common solicited systemic adverse events were irritability (49%), drowsiness (37%), and loss of appetite (29%). (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 ----------

- 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: 11/2016

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 aged 6 months 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
6 months 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)
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 sites for intramuscular injection are the anterolateral thigh for children aged 6 through 11 months and the deltoid muscle of the upper arm for persons aged 12 months and older. 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%).

In children aged 6 through 35 months who received FLULAVAL® QUADRIVALENT, the most common (≥10%) solicited local adverse reaction was pain (40%); the most common (≥10%) solicited systemic adverse events were irritability (49%), drowsiness (37%), and loss of appetite (29%).

<u>FLULAVAL in Adults</u>

Safety data were 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 U.S.-licensed trivalent, inactivated influenza vaccine, manufactured by Sanofi Pasteur Inc. (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 (NCT01389479) (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 U.S.-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 (NCT00232947) (Immunogenicity Non-Inferiority): Safety information was collected in a randomized, double-blind, active-controlled U.S. trial. The trial included 1,225 adults aged ≥50 years randomized to receive FLULAVAL (n = 610) or a U.S.-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 (NCT00216242) (Efficacy): Safety information was collected in a double-blind, placebo-controlled U.S. 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	
	Any	Gr 3[d]	Any	Gr 3[d]	Any	Gr 3[d]	Any	Gr 3[d]	Any	Gr 3[d]	Any	Gr 3[d]
Local Adverse Reactions												
Pain	24.1	0.0	30.5	0.4	24.9	0.0	31.7	0.0	51.1	0.2	13.8	<0.1
Redness	10.5	0.1	10.0	0.0	9.7	0.2	10.6	0.2	12.6	0.3	6.1	0.1
Swelling	9.8	0.1	10.4	0.4	6.9	0.3	9.4	0.5	11.0	0.3	2.8	0.0
Systemic Adverse Events												
Headache	17.6	0.4	17.2	0.0	11.0	0.2	12.0	0.3	18.1	0.6	18.7	0.5
Fatigue	17.1	0.3	15.4	0.0	12.0	0.2	13.0	0.5	20.1	0.6	17.7	0.4
Muscle aches[e]	12.9	0.4	15.8	0.0	11.0	0.2	10.2	0.0	18.3	0.2	10.2	0.2
Fever[f]	11.0	0.0	10.0	0.4	0.8	0.0	1.5	0.0	2.5	<0.1	1.4	0.1
Malaise	10.1	0.4	10.0	0.4	6.1	0.3	7.2	0.0	8.9	0.3	6.2	0.4
Sore throat	8.9	0.4	9.3	0.0	5.2	0.2	5.9	0.0	8.6	0.3	9.0	0.4
Reddened eyes	6.1	0.3	5.0	0.0	4.4	0.0	6.5	0.0	6.6	<0.1	6.0	<0.1
Cough	6.1	0.3	6.8	0.0	5.4	0.2	6.2	0.0	7.6	0.1	6.5	0.1
Chills	5.3	0.3	2.2	0.0	3.1	0.2	5.7	0.0	4.2	0.2	3.6	0.2
Chest tightness	3.3	0.0	1.4	0.0	2.5	0.3	2.1	0.0	3.4	<0.1	2.8	0.1
Facial swelling	1.0	0.0	0.4	0.0	1.3	0.0	1.6	0.0	1.3	0.0	1.0	0.0

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available. n = number of subjects with diary card completed. Gr 3 = Grade 3.

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

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

[c] U.S.-licensed trivalent, inactivated influenza vaccine (manufactured by Sanofi Pasteur Inc.).

[d] Grade 3 pain, headache, fatigue, muscle aches, malaise, sore throat, cough, chills, chest tightness: Defined as prevented work/school/normal activities.
Grade 3 redness, swelling: Defined as >50 mm. Grade 3 fever: Defined as >103.1°F (39.5°C).
Grade 3 reddened eyes: Defined as very reddened, interfered with vision or caused a doctor's visit. Grade 3 facial swelling: Defined as very swollen, prevented work/school/normal activities or caused a doctor's visit.

[e] For Trial 2 and Trial 3, includes muscle aches and arthralgia.
[f] Fever: Defined as ≥99.5°F (37.5°C).

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.

<u>FLULAVAL in Children</u>

Trial 4 (NCT00980005) (Immunogenicity Non-Inferiority): An observer-blind, active-controlled U.S. trial evaluated subjects aged 3 through 17 years who received FLULAVAL (n = 1,055) or FLUZONE (n = 1,061), a U.S.-licensed trivalent, inactivated influenza vaccine, manufactured by Sanofi Pasteur Inc. 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] %	
	Any	Grade 3[d]	Any	Grade 3[d]
	Aged 3 through 17 Years			
Local Adverse Reactions	**n = 1,042**		**n = 1,026**	
Pain	55.9	1.9	53.0	2.0
Redness	4.0	0.2	4.5	0.0
Swelling	4.4	0.1	4.9	0.0
	Aged 3 through 4 Years			
Systemic Adverse Events	**n = 293**		**n = 279**	
Irritability	25.3	1.7	26.5	1.1
Drowsiness	18.8	1.4	18.6	0.4
Loss of appetite	16.0	2.4	13.3	0.4
Fever[e]	5.1	1.0	2.9	0.4
	Aged 5 through 17 Years			
Systemic Adverse Events	**n = 750**		**n = 747**	
Muscle aches	23.9	0.7	22.9	0.9
Headache	16.8	0.8	15.3	0.5
Fatigue	16.8	1.3	16.7	1.2
Arthralgia	7.7	0.3	9.5	0.3
Shivering	5.6	0.1	4.8	0.4
Fever[e]	4.5	1.6	4.1	1.5

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available. n = number of subjects with diary card completed.

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

[b] Trial 4: NCT00980005.

[c] U.S.-licensed trivalent, inactivated influenza vaccine (manufactured by Sanofi Pasteur Inc.).

[d] Grade 3 pain: Defined as cried when limb was moved/spontaneously painful (children <5years), or pain that prevented normal activity (children ≥5 years).
Grade 3 swelling, redness: Defined as >100 mm.
Grade 3 irritability, drowsiness, muscle aches, headache, fatigue, arthralgia, shivering: Defined as prevented normal activity.
Grade 3 loss of appetite: Defined as not eating at all.
Grade 3 (or higher) fever: Defined as ≥102.2°F (39.0°C).

[e] Fever: Defined as ≥100.4°F (38.0°C)

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.

FLULAVAL QUADRIVALENT in Children

Safety data were obtained with FLULAVAL QUADRIVALENT in children aged 6 through 35 months. FLULAVAL QUADRIVALENT, an inactivated influenza vaccine that contains the hemagglutinins of 2 influenza A subtype viruses and 2 influenza type B viruses, is manufactured according to the same process as FLULAVAL.

Trial 5 (NCT02242643) was a randomized, observer-blind, active-controlled immunogenicity and safety trial. The trial included subjects aged 6 through 35 months who received FLULAVAL QUADRIVALENT (n = 1,207) or FLUZONE® QUADRIVALENT, a U.S.-licensed inactivated influenza vaccine (n = 1,217) used as comparator, manufactured by Sanofi Pasteur Inc. Children with no history of influenza vaccination received 2 doses of FLULAVAL QUADRIVALENT or the comparator vaccine approximately 28 days apart. Children with a history of influenza vaccination received one dose of FLULAVAL QUADRIVALENT or the comparator vaccine. In the overall population, 53% were male; 64% were white, 16% were black, 3% were Asian, and 17% were of other racial/ethnic groups. The mean age of subjects was 20 months. Subjects were followed for safety for 6 months; solicited local adverse reactions and systemic adverse events were collected for 7 days (day of vaccination and the next 6 days) postvaccination. The incidence of local adverse reactions and systemic adverse events occurring within 7 days of vaccination in children are shown in Table 4.

Table 4. FLULAVAL QUADRIVALENT: Incidence of Solicited Local Adverse Reactions and Systemic Adverse Events within 7 Days[a] of First Vaccination in Children Aged 6 through 35 Months[b] (Total Vaccinated Cohort)

	FLULAVAL QUADRIVALENT %		Active Comparator[c] %	
	Any	Grade 3[d]	Any	Grade 3[d]
Local Adverse Reactions	**n = 1,151**		**n = 1,146**	
Pain	40.3	2.4	37.4	1.4
Swelling	1.0	0.0	0.4	0.0
Redness	1.3	0.0	1.3	0.0
Systemic Adverse Events	**n = 1,155**		**n = 1,148**	
Irritability	49.4	3.8	45.9	3.0
Drowsiness	36.7	2.7	36.9	2.6
Loss of appetite	28.9	1.6	28.6	1.3
Fever [e]	5.6	1.4	5.8	1.0

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available (i.e., diary card completed for solicited symptoms). n = number of subjects with diary card completed.

[a] 7 days included day of vaccination and the subsequent 6 days.

[b] Trial 5: NCT02242643.

[c] U.S.-licensed quadrivalent, inactivated influenza vaccine (manufactured by Sanofi Pasteur Inc.).

[d] Grade 3 pain: Defined as cried when limb was moved/spontaneously painful.
Grade 3 swelling, redness: Defined as >100 mm.
Grade 3 irritability: Defined as crying that could not be comforted/prevented normal activity.
Grade 3 drowsiness: Defined as prevented normal activity.
Grade 3 loss of appetite: Defined as not eating at all.
Grade 3 (or higher) fever: Defined as >102.2°F (39.0°C).

[e] Fever: Defined as ≥100.4°F (38.0°C).

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

Unsolicited adverse events occurring within 28 days of vaccination were reported in 46% and 44% of subjects who received FLULAVAL QUADRIVALENT (n = 1,207) and the comparator vaccine (n = 1,217), respectively. The unsolicited adverse reactions that occurred most frequently (≥1%) for FLULAVAL QUADRIVALENT included upper respiratory tract infection, cough, diarrhea, pyrexia, vomiting, and rash. Serious adverse events occurring during the study period (approximately 6 months) were reported in 2% of subjects who received FLULAVAL

QUADRIVALENT and in 2% of subjects who received the comparator vaccine. There were no deaths reported during the study period.

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 were included based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to FLULAVAL.

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 Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FLULAVAL during pregnancy. Healthcare providers are encouraged to register women by calling 1-888-452-9622.

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

There are insufficient data on FLULAVAL in pregnant women to inform vaccine-associated risks.

A developmental toxicity study was performed in female rats administered FLULAVAL prior to mating and during gestation. The total dose was 0.2 mL at each occasion (a single human dose is 0.5 mL). This study revealed no adverse effects on fetal or pre-weaning development due to FLULAVAL *[see Data]*.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk: Pregnant women infected with seasonal

influenza are at increased risk of severe illness associated with influenza infection compared with non-pregnant women. Pregnant women with influenza may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.

Data

Animal Data: In a developmental toxicity study, female rats were administered FLULAVAL by intramuscular injection 4 weeks prior to mating, and on gestation Days 6, 8, 11, and 15. The total dose was 0.2 mL at each occasion (a single human dose is 0.5 mL). No adverse effects on pre-weaning development up to post-natal Day 25 were observed. There were no vaccine-related fetal malformations or variations.

8.2 Lactation

Risk Summary

It is not known whether FLULAVAL is excreted in human milk. Data are not available to assess the effects of FLULAVAL on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FLULAVAL and any potential adverse effects on the breastfed child from FLULAVAL or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness of FLULAVAL in children younger than 6 months have not been established.

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 xxxx-xxxx 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/xxxx (H1N1), A/xxxx (H3N2), and B/xxxx.

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

FLULAVAL has not been evaluated for carcinogenic, mutagenic potential, or male infertility in

animals. Vaccination of female rats with FLULAVAL had no effect on fertility *[see Use in Specific Populations (8.1)]*.

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 and FLULAVAL QUADRIVALENT.

14.1 Efficacy against Influenza

Efficacy Trial in Children

The efficacy of FLULAVAL QUADRIVALENT was evaluated in Trial 6, 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 5).

Table 5. 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 6: 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 6.

Table 6. 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 6: 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 7). 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 7. 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 U.S.-licensed trivalent, inactivated influenza vaccine, FLUZONE (manufactured by Sanofi Pasteur Inc.), intramuscularly; 959 subjects had complete serological data and no major protocol deviations *[see Adverse Reactions (6.1)]*.

Analyses of immunogenicity (Table 8) 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 8. 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 U.S.-licensed trivalent, inactivated influenza vaccine, FLUZONE, manufactured by Sanofi Pasteur Inc. 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 9). Within each age stratum, immunogenicity results were similar between the groups.

Table 9. 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] U.S.-licensed trivalent, inactivated influenza vaccine (manufactured by Sanofi Pasteur Inc.).

[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 U.S.-licensed trivalent, inactivated influenza vaccine (n = 979), manufactured by Sanofi Pasteur Inc., 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 with 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 10).

Table 10. 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] U.S.-licensed trivalent, inactivated influenza vaccine (Sanofi Pasteur Inc.).

[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%).

Trial 5 was a randomized, observer-blind, active-controlled trial in children aged 6 through 35 months which was conducted in the United States and Mexico. In this trial, subjects received 0.5 mL of FLULAVAL QUADRIVALENT containing 15 mcg HA of each of the four influenza strains included in the vaccine (n = 1,207); or 0.25 mL of control vaccine FLUZONE QUADRIVALENT (Influenza Vaccine) containing 7.5 mcg HA of each of the four influenza strains included in the vaccine (n = 1,217) *[see Adverse Reactions (6.1)]*.

Immune responses, specifically HI antibody titers to each virus strain in the vaccine, were evaluated in sera obtained 28 days following completion of vaccination regimen. Previously vaccinated children received one dose and previously unvaccinated children (i.e., unprimed individuals) received 2 doses 4 weeks apart of FLULAVAL QUADRIVALENT or the comparator. The immunogenicity endpoints were GMTs adjusted for baseline, and the percentage of subjects who achieved seroconversion, defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer ≥1:40 or at least a 4-fold increase in serum HI titer over baseline to ≥1:40, following vaccination, performed on the ATP cohort. FLULAVAL QUADRIVALENT was non-inferior to the comparator for all 4 vaccine strains based on adjusted GMTs and seroconversion rates (Table 11).

Table 11. Non-inferiority of FLULAVAL QUADRIVALENT Relative to Comparator Quadrivalent Influenza Vaccine at 28 Days Post-vaccination in Children Aged 6 through 35 Months[a] (According-to-Protocol Cohort for Immunogenicity)[b]

	FLULAVAL QUADRIVALENT[c]	Active Comparator[d]
Adjusted Geometric Mean Titers Against	**n = 972-974**	**n = 980**
A/California/07/2009 (H1N1)	99.6[e]	85.1
A/Texas/50/2012 (H3N2)	99.8[e]	84.6
B/Massachusetts/02/2012 (Yamagata lineage)	258.1[e]	167.3
B/Brisbane/60/2008 (Victoria lineage)	54.5[e]	33.7
Seroconversion[f] to:	**n = 972-974 % (95% CI)**	**n = 980 % (95% CI)**
A/California/07/2009 (H1N1)	73.7[e] (70.8, 76.4)	67.3 (64.3, 70.3)
A/Texas/50/2012 (H3N2)	76.1[e] (73.3, 78.8)	69.4 (66.4, 72.3)
B/Massachusetts/02/2012 (Yamagata lineage)	85.5[e] (83.2, 87.7)	73.8 (70.9, 76.5)
B/Brisbane/60/2008 (Victoria lineage)	64.9[e] (61.8, 67.9)	48.5 (45.3, 51.6)

CI = Confidence Interval.

[a] Trial 5: NCT02242643.

[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] A 0.5-mL dose containing 15 mcg each of A/California/07/2009 (H1N1), A/Texas/50/2012 (H3N2), B/Massachusetts/02/2012 (Yamagata lineage), and B/Brisbane/60/2008 (Victoria lineage).

[d] A 0.25-mL dose of U.S.-licensed quadrivalent, inactivated influenza vaccine (manufactured by Sanofi Pasteur Inc.) containing 7.5 mcg each of A/California/07/2009 (H1N1), A/Texas/50/2012 (H3N2), B/Massachusetts/02/2012 (Yamagata lineage), and B/Brisbane/60/2008 (Victoria lineage).

[e] Non-inferior to the comparator vaccine based on adjusted GMTs [upper limit of the 2-sided 95% CI for the GMT ratio (comparator/FLULAVAL QUADRIVALENT) ≤1.5] and seroconversion rates (upper limit of the 2-sided 95% CI on difference of comparator vaccine minus FLULAVAL QUADRIVALENT ≤10%).

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

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.

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 xxxxx-xxx-xx Syringe in Package of 10: NDC xxxxx-xxx-xx

NDC xxxxx-xxx-xx Multi-Dose Vial (containing 10 doses) in Package of 1: NDC xxxxx-xxx-xx

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.
- Encourage women exposed to FLULAVAL during pregnancy to enroll in the pregnancy registry *[see Use in Specific Populations (8.1)*.
- 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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FLV:XXPI