HIGHLIGHTS OF PRESCRIBING INFORMATION

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

FLULAVAL QUADRIVALENT (Influenza Vaccine)
Suspension for Intramuscular Injection
2016-2017 Formula
Initial U.S. Approval: 2013

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

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

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

FLULAVAL QUADRIVALENT is a vaccine indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. FLULAVAL QUADRIVALENT 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 QUADRIVALENT 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 QUADRIVALENT. 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 reaction was pain (60%); most common solicited systemic adverse events were muscle aches (26%), headache (22%), fatigue (22%), and arthralgia (15%). (6.1)
- In children aged 6 through 35 months, 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)
- In children aged 3 through 17 years, the most common (≥10%) solicited local adverse reaction was pain (65%). (6.1)
- In children aged 3 through 4 years, the most common (≥10%) solicited systemic adverse events were irritability (26%), drowsiness (21%), and loss of appetite (17%). (6.1)
- In children aged 5 through 17 years, the most common (≥10%) solicited systemic adverse events were muscle aches (29%), fatigue (22%), headache (22%), arthralgia (13%), and gastrointestinal symptoms (10%). (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 QUADRIVALENT 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® QUADRIVALENT is indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. FLULAVAL QUADRIVALENT 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 QUADRIVALENT are presented in Table 1.

Table 1. FLULAVAL QUADRIVALENT: 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 QUADRIVALENT 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 QUADRIVALENT 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 QUADRIVALENT 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 QUADRIVALENT. 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 QUADRIVALENT.

5.4 Altered Immunocompetence

If FLULAVAL QUADRIVALENT 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 QUADRIVALENT may not protect all susceptible individuals.

5.6 Persons at Risk of Bleeding

As with other intramuscular injections, FLULAVAL QUADRIVALENT 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 QUADRIVALENT could reveal adverse reactions not observed in clinical trials.

In adults who received FLULAVAL QUADRIVALENT, the most common (≥10%) solicited local adverse reaction was pain (60%); the most common (≥10%) solicited systemic adverse events were muscle aches (26%), headache (22%), fatigue (22%), and arthralgia (15%).

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%).

In children aged 3 through 17 years who received FLULAVAL QUADRIVALENT, the most common (≥10%) solicited local adverse reaction was pain (65%). In children aged 3 through 4 years, the most common (≥10%) solicited systemic adverse events were irritability (26%), drowsiness (21%), and loss of appetite (17%). In children aged 5 through 17 years, the most common (≥10%) systemic adverse events were muscle aches (29%), fatigue (22%), headache (22%), arthralgia (13%), and gastrointestinal symptoms (10%).

FLULAVAL QUADRIVALENT has been administered in 8 clinical trials to 1,384 adults aged 18 years and older, 1,965 children aged 6 through 35 months, and 3,516 children aged 3 through 17 years.

FLULAVAL QUADRIVALENT in Adults

Trial 1 (NCT01196975) was a randomized, double-blind, active-controlled, safety and immunogenicity trial. In this trial, subjects received FLULAVAL QUADRIVALENT (n = 1,272), or one of two formulations of a comparator trivalent influenza vaccine (FLULAVAL, TIV-1, n = 213 or TIV-2, n = 218), each containing an influenza type B virus that

corresponded to one of the two B viruses in FLULAVAL QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). The population was aged 18 years and older (mean age: 50 years) and 61% were female; 61% of subjects were white, 3% were black, 1% were Asian, and 35% were of other racial/ethnic groups. Solicited adverse events were collected for 7 days (day of vaccination and the next 6 days). The incidence of local adverse reactions and systemic adverse events occurring within 7 days of vaccination in adults are shown in Table 2.

Table 2. FLULAVAL QUADRIVALENT: Incidence of Solicited Local Adverse Reactions and Systemic Adverse Events within 7 Days[a] of Vaccination in Adults Aged 18 Years and Older[b] (Total Vaccinated Cohort)

	FLULAVAL QUADRIVALENT[c] n = 1,260 %		**Trivalent Influenza Vaccine (TIV)**			
			TIV-1 (B Victoria)[d] n = 208 %		**TIV-2 (B Yamagata)[e] n = 216 %**	
	Any	Grade 3[f]	Any	Grade 3[f]	Any	Grade 3[f]
Local Adverse Reactions						
Pain	59.5	1.7	44.7	1.0	41.2	1.4
Swelling	2.5	0.0	1.4	0.0	3.7	0.0
Redness	1.7	0.0	2.9	0.0	1.4	0.0
Systemic Adverse Events						
Muscle aches	26.3	0.8	25.0	0.5	18.5	1.4
Headache	21.5	0.9	19.7	0.5	22.7	0.0
Fatigue	21.5	0.8	21.6	1.0	17.1	1.9
Arthralgia	14.8	0.8	16.7	1.0	14.6	2.9
Gastrointestinal symptoms[g]	9.3	0.8	10.1	1.9	6.9	0.5
Shivering	8.8	0.6	7.7	0.5	6.0	0.9
Fever[h]	1.3	0.4	0.5	0.0	1.4	0.5

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

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

[b] Trial 1: NCT01196975.

[c] Contained two A strains and two B strains, one of Victoria lineage and one of Yamagata lineage.

[d] Contained the same two A strains as FLULAVAL QUADRIVALENT and a B strain of Victoria lineage.

[e] Contained the same two A strains as FLULAVAL QUADRIVALENT and a B strain of Yamagata lineage.

[f] Grade 3 pain: Defined as significant pain at rest; prevented normal everyday activities.
Grade 3 swelling, redness: Defined as >100 mm.
Grade 3 muscle aches, headache, fatigue, arthralgia, gastrointestinal symptoms, shivering: Defined as prevented normal activity.
Grade 3 (or higher) fever: Defined as ≥102.2°F (39.0°C).

[g] Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

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

Unsolicited adverse events occurring within 21 days of vaccination were reported in 19%, 23%, and 23% of subjects who received FLULAVAL QUADRIVALENT (n = 1,272), TIV-1 (B Victoria) (n = 213), or TIV-2 (B Yamagata) (n = 218), respectively. The unsolicited adverse events that occurred most frequently (≥1% for FLULAVAL QUADRIVALENT) included nasopharyngitis, upper respiratory tract infection, headache, cough, and oropharyngeal pain. Serious adverse events occurring within 21 days of vaccination were reported in 0.4%, 0%, and 0% of subjects who received FLULAVAL QUADRIVALENT, TIV-1 (B Victoria), or TIV-2 (B Yamagata), respectively.

FLULAVAL QUADRIVALENT in Children

Trial 4 (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 3.

Table 3. 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 4: 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.

Trial 2 (NCT01198756) was a randomized, double-blind, active-controlled trial. In this trial, subjects received FLULAVAL QUADRIVALENT (n = 932) or one of two formulations of a comparator trivalent influenza vaccine [FLUARIX® (Influenza Vaccine), TIV-1 (B Victoria), n = 929 or TIV-2 (B Yamagata), n = 932], each containing an influenza type B virus that corresponded to one of the two B viruses in FLULAVAL QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). The population was aged 3 through 17 years (mean age: 9 years) and 53% were male; 65% were white, 13% were Asian, 9% were black, and 13% were of other racial/ethnic groups. 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 7 days (day of vaccination and the next 6 days). 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 3 through 17 Years[b] (Total Vaccinated Cohort)

	FLULAVAL QUADRIVALENT[c] %		Trivalent Influenza Vaccine (TIV) TIV-1 (B Victoria)[d] %		TIV-2 (B Yamagata)[e] %	
	Any	Grade 3[f]	Any	Grade 3[f]	Any	Grade 3[f]
	Aged 3 through 17 Years					
Local Adverse Reactions	**n = 913**		**n = 911**		**n = 915**	
Pain	65.4	3.2	54.6	1.8	55.7	2.4
Swelling	6.2	0.1	3.3	0.0	3.8	0.0
Redness	5.3	0.1	3.2	0.0	3.5	0.0
	Aged 3 through 4 Years					
Systemic Adverse Events	**n = 185**		**n = 187**		**n = 189**	
Irritability	25.9	0.5	16.6	0.0	21.7	1.6
Drowsiness	21.1	0.0	19.8	1.6	23.3	0.5
Loss of appetite	17.3	0.0	16.0	1.6	13.2	1.1
Fever[g]	4.9	0.5	5.9	1.1	3.7	1.6
	Aged 5 through 17 Years					
Systemic Adverse Events	**n = 727**		**n = 724**		**n = 725**	
Muscle aches	28.5	0.7	24.9	0.6	24.7	1.0
Fatigue	22.1	0.7	23.6	1.8	23.0	1.0
Headache	22.0	1.0	22.1	1.0	20.1	1.2
Arthralgia	12.9	0.4	11.9	0.6	10.5	0.1
Gastrointestinal symptoms[h]	9.6	1.0	9.7	1.0	9.0	0.7
Shivering	7.0	0.4	6.9	1.2	6.9	0.6
Fever[g]	1.9	0.6	3.6	1.1	2.5	0.3

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

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

[b] Trial 2: NCT01198756.

[c] Contained two A strains and two B strains, one of Victoria lineage and one of Yamagata lineage.

[d] Contained the same two A strains as FLULAVAL QUADRIVALENT and a B strain of Victoria lineage.

[e] Contained the same two A strains as FLULAVAL QUADRIVALENT and a B strain of Yamagata lineage.

[f] Grade 3 pain: Defined as cried when limb was moved/spontaneously painful (children <5 years), or significant pain at rest, prevented normal everyday activities (children ≥5 years). 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).
Grade 3 muscle aches, fatigue, headache, arthralgia, gastrointestinal symptoms, shivering: Defined as prevented normal activity.

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

[h] Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

In children who received a second dose of FLULAVAL QUADRIVALENT, FLUARIX TIV-1 (B Victoria), or TIV-2 (B Yamagata), the incidences of adverse events following the second dose were generally lower than those observed after the first dose.

Unsolicited adverse events occurring within 28 days of vaccination were reported in 30%, 31%, and 30% of subjects who received FLULAVAL QUADRIVALENT (n = 932), FLUARIX TIV-1 (B Victoria) (n = 929), or TIV-2 (B Yamagata) (n = 932), respectively. The unsolicited adverse events that occurred most frequently (≥1% for FLULAVAL QUADRIVALENT) included vomiting, pyrexia, bronchitis, nasopharyngitis, pharyngitis, upper respiratory tract infection, headache, cough, oropharyngeal pain, and rhinorrhea. Serious adverse events occurring within 28 days of any vaccination were reported in 0.1%, 0.2%, and 0.2% of subjects who received FLULAVAL QUADRIVALENT, FLUARIX TIV-1 (B Victoria), or TIV-2 (B Yamagata), respectively.

Trial 3 (NCT01218308) was a randomized, observer-blind, non-influenza vaccine-controlled trial evaluating the efficacy of FLULAVAL QUADRIVALENT. The trial included subjects aged 3 through 8 years who received FLULAVAL QUADRIVALENT (n = 2,584) 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 (this dosing regimen for HAVRIX is not a U.S.-licensed schedule). 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. Solicited local adverse reactions and systemic adverse events were collected for 7 days (day of vaccination and the next 6 days). The incidence of local adverse reactions and systemic adverse events occurring within 7 days of vaccination in children are shown in Table 5.

Table 5. FLULAVAL QUADRIVALENT: Incidence of Solicited Local Adverse Reactions and Systemic Adverse Events within 7 Days[a] of First Vaccination in Children Aged 3 through 8 Years[b] (Total Vaccinated Cohort)

	FLULAVAL QUADRIVALENT %		HAVRIX[c] %	
	Any	Grade 3[d]	Any	Grade 3[d]
	Aged 3 through 8 Years			
Local Adverse Reactions	**n = 2,546**		**n = 2,551**	
Pain	39.4	0.9	27.8	0.7
Swelling	1.0	0.0	0.3	0.0
Redness	0.4	0.0	0.2	0.0
	Aged 3 through 4 Years			
Systemic Adverse Events	**n = 898**		**n = 895**	
Loss of appetite	9.0	0.3	8.2	0.4
Irritability	8.1	0.4	7.5	0.1
Drowsiness	7.7	0.4	7.3	0.0
Fever[e]	3.8	1.2	4.4	1.3
	Aged 5 through 8 Years			
Systemic Adverse Events	**n = 1,648**		**n = 1,654**	
Muscle aches	12.0	0.1	9.7	0.2
Headache	10.5	0.4	10.6	0.8
Fatigue	8.4	0.1	7.1	0.3
Arthralgia	6.3	0.1	4.5	0.1
Gastrointestinal symptoms[f]	5.5	0.2	5.9	0.3
Shivering	3.0	0.1	2.5	0.1
Fever[e]	2.7	0.6	2.7	0.7

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

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

[b] Trial 3: NCT01218308.

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

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

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

[f] Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

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

The frequency of unsolicited adverse events occurring within 28 days of vaccination was similar in both groups (33% for both FLULAVAL QUADRIVALENT and HAVRIX). The unsolicited adverse events that occurred most frequently (≥1% for FLULAVAL QUADRIVALENT) included diarrhea, pyrexia, gastroenteritis, nasopharyngitis, upper respiratory tract infection, varicella, cough, and rhinorrhea. Serious adverse events occurring within 28 days of any vaccination were reported in 0.7% of subjects who received FLULAVAL QUADRIVALENT and in 0.2% of subjects who received HAVRIX.

6.2 Postmarketing Experience

The following adverse events have been spontaneously reported during postapproval use of FLULAVAL QUADRIVALENT or FLULAVAL (trivalent influenza vaccine). 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 QUADRIVALENT or FLULAVAL.

Blood and Lymphatic System Disorders: Lymphadenopathy.

Eye Disorders: Eye pain, photophobia.

Gastrointestinal Disorders: Dysphagia, vomiting.

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

Immune System Disorders: Allergic 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, localized or generalized rash, pruritus, sweating.

Vascular Disorders: Flushing, pallor.

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

FLULAVAL QUADRIVALENT 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 QUADRIVALENT 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 QUADRIVALENT.

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 QUADRIVALENT 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 QUADRIVALENT in pregnant women to inform vaccine-associated risks.

A developmental toxicity study was performed in female rats administered FLULAVAL QUADRIVALENT prior to mating and during gestation and lactation periods. 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 QUADRIVALENT *[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 QUADRIVALENT by intramuscular injection 4 and 2 weeks prior to mating, on gestation Days 3, 8, 11, and 15, and on lactation Day 7. 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 QUADRIVALENT is excreted in human milk. Data are not available to assess the effects of FLULAVAL QUADRIVALENT 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 QUADRIVALENT and any potential adverse effects on the breastfed child from FLULAVAL QUADRIVALENT 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 QUADRIVALENT in children younger than 6 months have not been established.

8.5 Geriatric Use

In a randomized, double-blind, active-controlled trial, immunogenicity and safety were evaluated in a cohort of subjects aged 65 years and older who received FLULAVAL QUADRIVALENT (n = 397); approximately one-third of these subjects were aged 75 years and older. In subjects aged 65 years and older, the geometric mean antibody titers (GMTs) post-vaccination and seroconversion rates were lower than in younger subjects (aged 18 to 64 years) and the frequencies of solicited and unsolicited adverse events were generally lower than in younger subjects *[see Adverse Reactions (6.1), Clinical Studies (14.2)]*.

11 DESCRIPTION

FLULAVAL QUADRIVALENT, Influenza Vaccine, for intramuscular injection, is a quadrivalent, 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 QUADRIVALENT 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 QUADRIVALENT has been standardized according to USPHS requirements for the 2016-2017 influenza season and is formulated to contain 60 micrograms (mcg) hemagglutinin (HA) per 0.5-mL dose in the recommended ratio of 15 mcg HA of each of the following 4 viruses (two A strains and two B strains): A/California/7/2009 NYMC X-179A (H1N1), A/Hong Kong/4801/2014 (H3N2) NYMC X-263B, B/Phuket/3073/2013, and B/Brisbane/60/2008.

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 (≤320 mcg), and polysorbate 80 (≤887 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.

Public health authorities recommend influenza vaccine strains annually. Inactivated influenza vaccines are standardized to contain the hemagglutinins of strains representing the influenza viruses likely to circulate in the United States during the influenza season.

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.

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 QUADRIVALENT has not been evaluated for carcinogenic, mutagenic potential, or male infertility in animals. Vaccination of female rats with FLULAVAL QUADRIVALENT had no effect on fertility *[see Use in Specific Populations (8.1)]*.

14 CLINICAL STUDIES

14.1 Efficacy against Influenza

The efficacy of FLULAVAL QUADRIVALENT was evaluated in Trial 3, 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 (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 *[see Adverse Reactions (6.1)]*. 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 6).

Table 6. 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 3: 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 7.

Table 7. 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 3: 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.

14.2 Immunological Evaluation

Adults

Trial 1 was a randomized, double-blind, active-controlled, safety and immunogenicity trial conducted in subjects aged 18 years and older. In this trial, subjects received FLULAVAL QUADRIVALENT (n = 1,246) or one of two formulations of a comparator trivalent influenza vaccine (FLULAVAL, TIV-1, n = 204 or TIV-2, n = 211), each containing an influenza type B virus that corresponded to one of the two B viruses in FLULAVAL QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage) *[see Adverse Reactions (6.1)]*.

Immune responses, specifically hemagglutination inhibition (HI) antibody titers to each virus strain in the vaccine, were evaluated in sera obtained 21 days after administration of FLULAVAL QUADRIVALENT or the comparators. The immunogenicity endpoint was GMTs adjusted for baseline, performed on the According-to-Protocol (ATP) cohort for whom immunogenicity assay results were available after vaccination. FLULAVAL QUADRIVALENT was non-inferior to both TIVs based on adjusted GMTs (Table 8). The antibody response to influenza B strains contained in FLULAVAL QUADRIVALENT was higher than the antibody response after vaccination with a TIV containing an influenza B strain from a different lineage. There was no evidence that the addition of the second B strain resulted in immune interference to other strains included in the vaccine (Table 8).

Table 8. Non-inferiority of FLULAVAL QUADRIVALENT Relative to Trivalent Influenza Vaccine (TIV) 21 Days Post-vaccination in Adults Aged 18 Years and Older[a] (According-to-Protocol Cohort for Immunogenicity)[b]

Geometric Mean Titers Against	FLULAVAL QUADRIVALENT[c] n = 1,245-1,246 (95% CI)	TIV-1 (B Victoria)[d] n = 204 (95% CI)	TIV-2 (B Yamagata)[e] n = 210-211 (95% CI)
A/California/7/2009 (H1N1)	204.6[f] (190.4, 219.9)	176.0 (149.1, 207.7)	149.0 (122.9, 180.7)
A/Victoria/210/2009 (H3N2)	125.4[f] (117.4, 133.9)	147.5 (124.1, 175.2)	141.0 (118.1, 168.3)
B/Brisbane/60/2008 (Victoria lineage)	177.7[f] (167.8, 188.1)	135.9 (118.1, 156.5)	71.9 (61.3, 84.2)
B/Florida/4/2006 (Yamagata lineage)	399.7[f] (378.1, 422.6)	176.9 (153.8, 203.5)	306.6 (266.2, 353.3)

CI = Confidence Interval.

[a] Trial 1: NCT01196975.

[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] Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Florida/04/2006 (Yamagata lineage), and B/Brisbane/60/2008 (Victoria lineage)

[d] Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage)

[e] Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage).

[f] Non-inferior to both TIVs based on adjusted GMTs [upper limit of the 2-sided 95% CI for the GMT ratio (TIV/FLULAVAL QUADRIVALENT) ≤1.5]; superior to TIV-1 (B Victoria) with respect to the B strain of Yamagata lineage and to TIV-2 (B Yamagata) with respect to the B strain of Victoria lineage based on adjusted GMTs [lower limit of the 2-sided 95% CI for the GMT ratio (FLULAVAL QUADRIVALENT/TIV) >1.5].

Children

Trial 4 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 two 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 9).

Table 9. 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]

Adjusted Geometric Mean Titers Against	FLULAVAL QUADRIVALENT[c] n = 972-974	Active Comparator[d] 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 4: 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.

Trial 2 was a randomized, double-blind, active-controlled trial conducted in children aged 3 through 17 years. In this trial, subjects received FLULAVAL QUADRIVALENT (n = 878), or one of two formulations of a comparator trivalent influenza vaccine (FLUARIX, TIV-1, n = 871 or TIV-2 n = 878), each containing an influenza type B virus that corresponded to one of the two B viruses in FLULAVAL QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage) *[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 one or 2 doses of FLULAVAL QUADRIVALENT or the comparators. The immunogenicity 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 ATP cohort. FLULAVAL QUADRIVALENT was non-inferior to both TIVs based on adjusted GMTs and seroconversion rates (Table 10). The antibody response to influenza B strains contained in FLULAVAL QUADRIVALENT was higher than the antibody response after vaccination with a TIV containing an influenza B strain from a different lineage. There was no evidence that the addition of the second B strain resulted in immune interference to other strains included in the vaccine (Table 10).

Table 10. Non-inferiority of FLULAVAL QUADRIVALENT Relative to Trivalent Influenza Vaccine (TIV) at 28 Days Post-vaccination in Children Aged 3 through 17 Years[a] (According-to-Protocol Cohort for Immunogenicity)[b]

	FLULAVAL QUADRIVALENT[c]	TIV-1 (B Victoria)[d]	TIV-2 (B Yamagata)[e]
Geometric Mean Titers Against	**n = 878 (95% CI)**	**n = 871 (95% CI)**	**n = 877-878 (95% CI)**
A/California/7/2009 (H1N1)	362.7[f] (335.3, 392.3)	429.1 (396.5, 464.3)	420.2 (388.8, 454.0)
A/Victoria/210/2009 (H3N2)	143.7[f] (134.2, 153.9)	139.6 (130.5, 149.3)	151.0 (141.0, 161.6)
B/Brisbane/60/2008 (Victoria lineage)	250.5[f] (230.8, 272.0)	245.4 (226.9, 265.4)	68.1 (61.9, 74.9)
B/Florida/4/2006 (Yamagata lineage)	512.5[f] (477.6, 549.9)	197.0 (180.7, 214.8)	579.0 (541.2, 619.3)
Seroconversion[g] to:	**n = 876 % (95% CI)**	**n = 870 % (95% CI)**	**n = 876-877 % (95% CI)**
A/California/7/2009 (H1N1)	84.4[f] (81.8, 86.7)	86.8 (84.3, 89.0)	85.5 (83.0, 87.8)
A/Victoria/210/2009 (H3N2)	70.1[f] (66.9, 73.1)	67.8 (64.6, 70.9)	69.6 (66.5, 72.7)
B/Brisbane/60/2008 (Victoria lineage)	74.5[f] (71.5, 77.4)	71.5 (68.4, 74.5)	29.9 (26.9, 33.1)
B/Florida/4/2006 (Yamagata lineage)	75.2[f] (72.2, 78.1)	41.3 (38.0, 44.6)	73.4 (70.4, 76.3)

CI = Confidence Interval.

[a] Trial 2: NCT01198756.

[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] Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Florida/04/2006 (Yamagata lineage), and B/Brisbane/60/2008 (Victoria lineage).

[d] Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage).

[e] Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage).

[f] Non-inferior to both TIVs based on adjusted GMTs [upper limit of the 2-sided 95% CI for the GMT ratio (TIV/FLULAVAL QUADRIVALENT) ≤1.5] and seroconversion rates (upper limit of the 2-sided 95% CI on difference of the TIV minus FLULAVAL QUADRIVALENT ≤10%); superior to TIV-1 (B Victoria) with respect to the B strain of Yamagata lineage and to TIV-2 (B Yamagata) with respect to the B strain of Victoria lineage based on adjusted GMTs

[lower limit of the 2-sided 95% CI for the GMT ratio (FLULAVAL QUADRIVALENT/TIV) >1.5] and seroconversion rates (lower limit of the 2-sided 95% CI on difference of FLULAVAL QUADRIVALENT minus the TIV >10%).

[g] 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 QUADRIVALENT 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 19515-908-41 Syringe in Package of 10: NDC 19515-908-52

NDC 19515-903-01 Multi-Dose Vial (containing 10 doses) in Package of 1: NDC 19515-903-11

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 QUADRIVALENT.
- Educate regarding potential side effects, emphasizing that (1) FLULAVAL QUADRIVALENT contains non-infectious killed viruses and cannot cause influenza, and (2) FLULAVAL QUADRIVALENT 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 QUADRIVALENT 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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