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Supporting Influenza Vaccination in the Older Adult Population in the Community Pharmacy

AS HEALTHCARE PROFESSIONALS EMBEDDED WITHIN the community, pharmacists administer vaccines that help provide protection against infectious diseases, such as influenza, through advocating for vaccination.

Pharmacists are well-positioned to recognize the specific immunization needs of adults aged 65 and older and administer the most appropriate influenza vaccine option. The immune system can deteriorate as adults grow older and this population may not respond as well to vaccination.¹ Moreover, adults aged 65 and older are at increased risk of developing serious influenza-related complications (eg, hospitalization and death) compared with younger adults.¹

Influenza vaccine coverage rates are not ideal in older adults; however, of adults who do receive an influenza vaccination, 39% receive it in a pharmacy.² Pharmacists have an important opportunity to increase vaccine coverage rates by identifying vaccination opportunities in vulnerable populations, such as when older adults with chronic illnesses visit the pharmacy for prescription pick up.

When choosing among the influenza vaccines, it is important to be aware of options that have proven efficacy and effectiveness to help protect against influenza infection and help prevent influenza-related complications in adults 65 years and older.

RECOMMENDATIONS FROM THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

On June 22, 2022, the US Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) proposed recommendations that adults aged 65 years and older preferentially receive 1 of the following influenza vaccines: quadrivalent high-dose inactivated influenza vaccine (HD-IIV4), quadrivalent recombinant influenza vaccine (RIV4), or quadrivalent adjuvanted inactivated influenza vaccine (aIIV4). If none of these 3 vaccines are available at an opportunity for vaccine administration, then any other age-appropriate influenza vaccine should be used.³

Notably, there is no preference for any specific vaccine over another because there are limited data from studies or head-to-head, randomized control trials (RCTs) that directly compare the efficacy and effectiveness of the influenza vaccines that can be used to inform specific recommendations.⁴

Only Sanofi higher-dose flu shots are proven to

prevent more flu in older adults than a standard-dose influenza vaccine in RCTs.^{5,6}

FLUZONE® HIGH-DOSE QUADRIVALENT (INFLUENZA VACCINE)

Fluzone High-Dose Quadrivalent is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. It is approved for use in persons 65 years of age and older.⁵ Fluzone High-Dose Quadrivalent provides 4-strain protection against 2 influenza A strains (A[H3N2] and A[H1N1]) and both influenza B lineages (B Victoria lineage and B Yamagata lineage) that unpredictably co-circulate each season. It contains 4 times the amount of hemagglutinin (HA) antigen than in a standard-dose influenza vaccine (60 vs 15 micrograms per strain, respectively).^{5,6}

SELECT IMPORTANT SAFETY INFORMATION FOR FLUZONE® HIGH-DOSE QUADRIVALENT (INFLUENZA VACCINE)

Fluzone High-Dose Quadrivalent should not be administered to anyone who has had a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or after previous dose of any influenza vaccine.

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

Please see Important Safety Information throughout and at the end of this article.

Clinical evidence

Fluzone® High-Dose (Influenza Vaccine) trivalent formulation is the first and only high-dose influenza vaccine proven to provide superior flu protection in a clinical trial compared with standard-dose Fluzone® (Influenza Vaccine).⁵ The efficacy of the trivalent formulation is relevant to Fluzone® High-Dose Quadrivalent (Influenza Vaccine) since both vaccines are manufactured according to the same process and have overlapping compositions.⁵

In a randomized (1:1), controlled trial in adults aged 65 and older (N = 31,803) during the 2011-2012 and 2012-2013

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influenza seasons, Fluzone High-Dose (Influenza Vaccine) trivalent formulation provided 24% (95% CI, 10-37) better protection against influenza due to any laboratory-confirmed, circulating strain compared with standard-dose Fluzone (Influenza Vaccine). The prespecified statistical superiority criterion for the primary endpoint (lower limit of the 2-sided 95% CI of the vaccine efficacy of Fluzone High-Dose relative to Fluzone >9.1%) was met.^{5,6}

Safety

In a randomized (2:1), double-blind controlled immunogenicity and safety study in adults 65 and older, solicited injection-site reactions and systemic adverse reactions were slightly more frequent with vaccination with Fluzone High-Dose (Influenza Vaccine) trivalent formulation as compared with standard-dose Fluzone (Influenza Vaccine). The safety analysis set included 2573 Fluzone High-Dose (Influenza Vaccine) trivalent formulation recipients and 1260 standard-dose Fluzone (Influenza Vaccine) recipients. In adults aged 65 and older, the most common injection-site reactions (>10%) were pain and erythema; the most common solicited systemic adverse events were myalgia, headache, and malaise.^{5,7}

Immuno-bridging study

An immuno-bridging study compared the safety and immunogenicity of Fluzone High-Dose Quadrivalent with that of Fluzone High-Dose (trivalent formulation) during the 2017-2018 influenza season. A total of 2670 adults aged 65 years and older were randomized (4:1:1) to receive 1 dose of either Fluzone High-Dose Quadrivalent or 1 of 2 formulations of Fluzone High-Dose containing either influenza B Victoria or B Yamagata lineages.⁵ Fluzone High-Dose Quadrivalent induced a noninferior immune response compared with 2 Fluzone High-Dose formulations, as assessed by geometric mean antibody titers at day 28 and seroconversion rates, to strains common to formulations of both vaccines, based on pre-specified criteria.⁵

Fluzone High-Dose Quadrivalent exhibited a similar safety profile compared with Fluzone High-Dose formulations. Rates of any solicited local and systemic reactions, including grade 3 reactions, were similar among Fluzone High-Dose Quadrivalent and Fluzone High-Dose trivalent formulation recipients aged 65 years and older. The most common reactions occurring after Fluzone High-Dose Quadrivalent administration were injection-site pain (41.3%), myalgia (22.7%), headache (14.4%), and malaise (13.2%).⁵

Real-world evidence

A systematic review and meta-analysis was performed, which included data pooled from 15 published studies

conducted in approximately 34 million adults aged 65 years and older over 10 influenza seasons. Identified studies were conducted over the 2009-2010 to 2018-2019 influenza seasons; of which, 7 seasons were A (H3N2) predominant, 3 seasons were A (H1N1) predominant, and 3 seasons were antigenically mismatched.⁸ HD-IIV3 was more effective than standard-dose influenza vaccine at preventing pneumonia and influenza mortality (39.9%; 95% CI, 18.6-55.6), cardiorespiratory mortality (27.7%; 95% CI, 13.2-32.0), and post-influenza mortality (22.2%; 95% CI, -18.2-48.8).⁸ Additionally, HD-IIV3 was more effective than standard-dose influenza vaccine at preventing hospital admissions due to influenza illness (11.7%; 95% CI, 7.0-16.1), pneumonia (27.3%; 95% CI, 15.3-37.6), combined pneumonia and influenza (13.4%; 95% CI, 7.3-19.2), and cardiorespiratory events (17.9%; 95% CI, 15.0-20.8).

Select end points are presented in this article; however, influenza-like illness, all-cause hospitalizations, and all-cause mortality were also evaluated in this meta-analysis.⁸ Study limitations included the following: a high degree of statistical heterogeneity was observed, unmeasured confounders could have affected the results, most outcomes of the reviews were not lab-confirmed and do not necessarily represent strain-specific vaccine effectiveness, and the between studies weighting may have led to overall results that were significant while subanalyses had wider confidence intervals. Study funding was provided by Sanofi Pasteur and the authors were employees of Sanofi Pasteur.⁸

SELECT IMPORTANT SAFETY INFORMATION FOR FLUZONE® HIGH-DOSE QUADRIVALENT (INFLUENZA VACCINE) (Continued)

If Guillain-Barré syndrome has occurred within 6 weeks following previous influenza vaccination, the decision to give Fluzone High-Dose Quadrivalent should be based on careful consideration of the potential benefits and risks.

If Fluzone High-Dose Quadrivalent is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be lower than expected.

Please see Important Safety Information throughout and at the end of this article.

FLUBLOK® QUADRIVALENT (INFLUENZA VACCINE)

Flublok Quadrivalent is a vaccine indicated for active immunization against disease caused by influenza A subtype viruses and influenza type B viruses contained in the vac-

cine. Flublok Quadrivalent is approved for use in persons 18 years of age and older. It contains 3 times the amount of HA antigen than in a standard-dose influenza vaccine (45 vs 15 micrograms, respectively).¹¹ Recombinant technology may provide unique features to an influenza vaccine: it ensures the exact strain matches to World Health Organization and FDA-selected strains; avoids mutations in manufacturing that could lead to reduced vaccine effectiveness; and it may provide cross-protection by providing broader access to antigenic sites, allowing greater accessibility for an immune response.^{9,10}

SELECT IMPORTANT SAFETY INFORMATION FOR FLUBLOK® QUADRIVALENT (INFLUENZA VACCINE)

Flublok Quadrivalent should not be administered to anyone who has had a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine.

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

Please see Important Safety Information throughout and at the end of this article.

Clinical evidence

Flublok Quadrivalent is the first and only recombinant influenza vaccine proven to prevent more influenza in adults aged 50 years and older compared with a standard-dose quadrivalent influenza vaccine in a RCT.^{11,12} In a randomized (1:1), controlled trial that included approximately 9000 adults 50 years and older, Flublok Quadrivalent provided 30% (95% CI, 10-47) better protection against influenza due to any PCR-confirmed circulating strain versus a standard-dose quadrivalent inactivated influenza vaccine, Fluarix Quadrivalent® (Influenza Vaccine).^{11,12}

Safety

The rates of local and systemic adverse reactions were similar (within 7 days of administration) among Flublok Quadrivalent and Fluarix Quadrivalent® recipients.¹¹ For Flublok Quadrivalent, in adults aged 18 through 49, the most common (≥10%) injection-site reactions were tenderness (48%) and pain (37%); the most common (≥10%) solicited systemic adverse reactions were headache (20%), fatigue (17%), myalgia (13%), and arthralgia (10%).¹¹ In adults 50 years of age and older, the most common (≥10%) injection site reactions were tenderness (34%) and pain (19%); the most common (≥10%) solicited systemic adverse reactions were headache (13%) and fatigue (12%).¹¹

Real-world evidence

A retrospective observational cohort study analyzed Medicare fee-for-service claims from 12.7 million adults aged 65 and older who received an influenza vaccination during the 2019-2020 influenza season with 1 of the following vaccines: HD-IIV3 (n = ~7.1 million), egg-based, adjuvanted, standard-dose trivalent (aIIV3) (n = ~2.5 million), egg-based, standard-dose quadrivalent (IIV4) (n = ~1.5 million), cell-cultured standard-dose quadrivalent (cIIV4) (n = ~0.8 million), and RIV4 (n = ~0.6 million). Characteristics during the 2019-2020 season were: influenza A (H1N1) and influenza B (Victoria) were predominating strains with no significant circulation of influenza A (H3N2); an H1N1 strain with an amino acid change emerged late in the season and likely did not substantially affect the vaccine efficacy during the study period; trivalent vaccines contained the influenza B (Victoria) lineage.¹³

Results of this study showed that RIV4 (Flublok Quadrivalent) was associated with significantly fewer influenza hospital encounters compared with IIV4.¹⁶ The relative vaccine effectiveness against influenza hospital encounters with RIV4 (Flublok Quadrivalent) was 13.3% (95% CI, 7.4-18.9); HD-IIV3 (Fluzone® High-Dose trivalent [Influenza Vaccine]) was 6.8% (95% CI, 3.3-10.1), aIIV3 was 8.2% (95% CI, 4.2-12.0); and cIIV4 was 2.8% (95% CI, -2.8 to 8.2).⁹ These data correspond with 1 of 3 primary analyses. Two additional primary analyses were conducted; these 2 vaccine analyses compared cIIV4 with IIV4 and RIV4 with IIV4.¹³ Study limitations included the following: lack of access to virological case confirmation may have led to underestimation of the magnitude of differences, residual confounding by unmeasured covariates could have affected the results, and the observation period was cut off at the end of February to avoid potential bias from the overlap between influenza season and the escalation of the COVID-19 pandemic in the United States.¹³ The authors of this study were affiliated with the FDA and Centers for Medicare and Medicaid Services.

SELECT IMPORTANT SAFETY INFORMATION FOR FLUBLOK® QUADRIVALENT (INFLUENZA VACCINE) (Continued)

If Guillain-Barré syndrome has occurred within 6 weeks following previous influenza vaccination, the decision to give Flublok Quadrivalent should be based on careful consideration of the potential benefits and risks.

If Flublok Quadrivalent is administered to immunocompromised persons, including those receiving immu-

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Please see full Prescribing Information for Flublok Quadrivalent and Fluzone High-Dose Quadrivalent at sanofi.com.

nosuppressive therapy, the immune response may be lower than expected.

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ROLE OF THE PHARMACIST

Providing counseling and strong recommendations for influenza vaccines in adults 65 and older is an important clinical priority in the community pharmacy setting. Influenza vaccination in older adults is associated with reduced severity of influenza illness and reduced risk of influenza-associated hospitalization.

Fluzone® High-Dose Quadrivalent (Influenza Vaccine) and Flublok® Quadrivalent (Influenza Vaccine) demonstrated better influenza protection versus a standard-dose influenza vaccine in randomized controlled efficacy trials in older adults.^{5,6,11,12} Real-world evidence demonstrated better protection against influenza-related complications versus standard-dose influenza vaccines in adults 65 and older.^{11,13}

IMPORTANT SAFETY INFORMATION FOR FLUBLOK® QUADRIVALENT (INFLUENZA VACCINE) AND FLUZONE® HIGH-DOSE QUADRIVALENT (INFLUENZA VACCINE)

Flublok Quadrivalent and Fluzone High-Dose Quadrivalent should not be administered to anyone who has had a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine (including egg protein for Fluzone High-Dose Quadrivalent). In addition, Fluzone High-Dose Quadrivalent should not be administered to anyone who has had a severe allergic reaction after previous dose of any influenza vaccine.

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

If Guillain-Barré syndrome has occurred within 6 weeks following previous influenza vaccination, the decision to give Flublok Quadrivalent and Fluzone High-Dose Quadrivalent should be based on careful consideration of the potential benefits and risks.

If Flublok Quadrivalent and Fluzone High-Dose Quadrivalent are administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be lower than expected.

Vaccination with Flublok Quadrivalent and Fluzone High-Dose Quadrivalent may not protect all recipients.

Please see Important Safety Information throughout and at the end of this article and Brief Summary of Prescribing Information for Flublok Quadrivalent (Influenza Vaccine) and Fluzone High-Dose Quadrivalent (Influenza Vaccine) on adjacent pages.

Please see full Prescribing Information for Flublok Quadrivalent and Fluzone High-Dose Quadrivalent at sanofflu.com.

For Flublok Quadrivalent, in adults 18 through 49 years of age, the most common injection-site reactions were tenderness and pain; the most common solicited systemic adverse reactions were headache, fatigue, myalgia, and arthralgia. In adults 50 years of age and older, the most common injection-site reactions were tenderness and pain; the most common solicited systemic adverse reactions were headache, and fatigue.

For Fluzone High-Dose Quadrivalent, in adults 65 years of age and older, the most common injection-site reaction was pain; the most common solicited systemic adverse reactions were myalgia, headache, and malaise.

For Flublok Quadrivalent and Fluzone High-Dose Quadrivalent, other adverse reactions may occur.

Please see Brief Summary of Prescribing Information of Flublok Quadrivalent (Influenza Vaccine) and Fluzone High-Dose Quadrivalent (Influenza Vaccine) on adjacent pages.

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Flublok® Quadrivalent (Influenza Vaccine), Sterile Solution for Intramuscular Injection 2022-2023 Formula Rx Only

Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

Flublok Quadrivalent is a vaccine indicated for active immunization against disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. Flublok Quadrivalent is approved for use in persons 18 years of age and older [see *Clinical Studies (14) in the full prescribing information*].

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Dosage

Administer Flublok Quadrivalent as a single 0.5 mL dose.

2.2 Administration

Invert the prefilled syringe containing Flublok Quadrivalent gently prior to affixing the appropriate size needle for intramuscular 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.

The preferred site for injection is the deltoid muscle. Flublok Quadrivalent should not be mixed in the same syringe with any other vaccine.

4 CONTRAINDICATIONS

Flublok Quadrivalent is contraindicated in individuals with known severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine [see *Postmarketing Experience (6.2) and Description (11) in the full prescribing information*].

5 WARNINGS AND PRECAUTIONS

5.1 Managing Allergic Reactions

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

5.2 Guillain Barré Syndrome

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain Barré Syndrome (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 per 1 million persons vaccinated. If GBS has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give Flublok should be based on careful consideration of the potential benefits and risks.

5.3 Altered Immunocompetence

If Flublok Quadrivalent is administered to immunocompromised individuals, including persons receiving immunosuppressive therapy, the immune response may be diminished.

5.4 Limitations of Vaccine Effectiveness

Vaccination with Flublok Quadrivalent may not protect all vaccine recipients.

6 ADVERSE REACTIONS

In adults 18 through 49 years of age, the most common (≥10%) injection-site reactions were tenderness (48%) and pain (37%); the most common (≥10%) solicited systemic adverse reactions were headache (20%), fatigue (17%), myalgia (13%), and arthralgia (10%) [see *Clinical Trials Experience (6.1)*].

In adults 50 years of age and older, the most common (≥10%) injection site reactions were tenderness (34%) and pain (19%); the most common (≥10%) solicited systemic adverse reactions were headache (13%) and fatigue (12%) [see *Clinical Trials Experience (6.1)*].

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a vaccine cannot be directly compared to rates in the clinical studies of another vaccine and may not reflect the rates observed in clinical practice.

Flublok Quadrivalent

Flublok Quadrivalent has been administered to and safety data collected from 998 adults 18–49 years of age (Study 1) and 4328 adults 50 years of age and older (Study 2).

In Studies 1 and 2, local (injection site) and systemic adverse reactions were solicited with the use of a memory aid for 7 days following vaccination, unsolicited adverse events were collected for ~28 days post-vaccination, and serious adverse events (SAEs) were collected for 6 months post-vaccination via clinic visit or remote contact.

Study 1 included 1330 subjects 18 through 49 years of age for safety analysis, randomized to receive Flublok Quadrivalent (n=998) or a comparator inactivated influenza vaccine (Fluarix® Quadrivalent, manufactured by GlaxoSmithKline) (n=332) [see *Clinical Studies (14) in the full prescribing information*]. The mean age of participants was 33.5 years. Overall, 65% of subjects were female, 59% white/Caucasian, 37% black/African American, 1.0% Native Hawaiian/Pacific Islander, 0.8% American Indian/Alaskan Native, 0.5% Asian, 1.4% other racial groups, and 16% of Hispanic/Latino ethnicity. Table 1 summarizes the incidence of solicited local and systemic adverse reactions reported within seven days of vaccination with Flublok Quadrivalent or the comparator vaccine.

Table 1: Frequency of Solicited Local Injection Site Reactions and Systemic Adverse Reactions within 7 Days of Administration of Flublok Quadrivalent or Comparator[†] in Adults 18–49 Years of Age, Study 1 (Reactogenicity Populations)^{‡,†}

Reactogenicity Term	Flublok Quadrivalent N=996 %			Comparator N=332 %		
	Any Grade [‡]	Grade 3	Grade 4	Any Grade [‡]	Grade 3	Grade 4
Subjects with ≥1 injection site reaction ^{§,¶}	51	1	0	52	2	0
Local Tenderness	48	1	0	47	1	0
Local Pain	37	1	0	36	1	0
Firmness / Swelling	5	0	0	3	0	0
Redness	4	0	0	1	0	0
Subjects with ≥1 systemic reaction ^{§,¶}	34	2	<1	36	3	<1
Headache	20	1	0	21	2	<1
Fatigue	17	1	0	17	1	0
Muscle Pain	13	1	0	12	1	0
Joint Pain	10	1	0	10	1	0
Nausea	9	1	<1	9	1	0
Shivering / Chills	7	1	0	6	1	0
Fever ^{†, ¶}	2	<1	0	1	<1	0

NOTE: Data based on the most severe response reported by subjects. Results ≥1% reported to nearest whole percent; results >0 but <1% reported as <1%.

[†]Comparator = U.S.-licensed comparator quadrivalent inactivated influenza vaccine manufactured by GlaxoSmithKline.

[‡]Study 1 is registered as NCT02290509 under the National Clinical Trials registry.

[§]Denominators for fever: Flublok Quadrivalent n = 990, Comparator n = 327.

[¶]Reactogenicity Populations were defined as all randomized subjects who received study vaccine according to the treatment actually received and who had at least one non-missing data point for injection site, systemic or body temperature reactogenicity categories. For local pain, tenderness and systemic reactions: Grade 1 = No interference with activities. Grade 2 = Prevented some activities, and headache may have required non-narcotic pain reliever. Grade 3 = Prevented most or all normal activities or required prescription medications. Grade 4 = Required visit to ER or hospitalization. For injection site redness and firmness/swelling: Grade 1=25 to ≤50 mm (small). Grade 2=51 to ≤100 mm (medium). Grade 3=>100 mm (large). Grade 4=necrosis or exfoliative dermatitis.

^{¶¶}Denominators for injection site reactions: Flublok Quadrivalent n = 996, Comparator n = 332.

^{¶¶¶}Denominators for systemic reactions: Flublok Quadrivalent n = 994, Comparator n = 332.

^{¶¶¶¶}Fever defined as ≥100.4°F (38°C). Grade 1 (≥100.4°F to ≤101.1°F); Grade 2 (101.2°F to ≤102.0°F); Grade 3 (102.1°F to ≤104°F). Grade 4 >104°F.

Study 2 included 8672 subjects 50 years of age and older for safety analysis, randomized to receive Flublok Quadrivalent (n=4328) or Comparator (Fluarix Quadrivalent, manufactured by GlaxoSmithKline) as an active control (n=4344) [see *Clinical Studies (14) in the full prescribing information*]. The mean age of participants was 62.7 years. Overall, 58% of subjects were female, 80% white/Caucasian, 18% black/African American, 0.9% American Indian/Alaskan Native, 0.4% Asian, 0.2% Native Hawaiian/Pacific Islander, 0.7% other racial groups, and 5% of Hispanic/Latino ethnicity. Table 2 summarizes the incidence of solicited local and systemic adverse reactions reported within seven days of vaccination with Flublok Quadrivalent or Comparator.

Table 2: Frequency of Solicited Local Injection Site Reactions and Systemic Adverse Reactions within 7 Days of Administration of Flublok Quadrivalent or Comparator[†] in Adults 50 Years of Age and Older, Study 2 (Reactogenicity Populations)^{‡,†}

Reactogenicity Term	Flublok Quadrivalent N=4312 %			Comparator N=4327 %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Subjects with ≥1 injection site reaction ^{§,¶}	38	<1	<1	40	<1	<1

Table 2: Frequency of Solicited Local Injection Site Reactions and Systemic Adverse Reactions within 7 Days of Administration of Flublok Quadrivalent or Comparator in Adults 50 Years of Age and Older, Study 2 (Reactogenicity Populations)^{†, ‡} (continued)

Reactogenicity Term	Flublok Quadrivalent N=4312 %			Comparator N=4327 %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Local Tenderness	34	<1	<1	37	<1	<1
Local Pain	19	<1	0	22	<1	<1
Firmness / Swelling	3	<1	0	3	<1	0
Redness	3	<1	0	2	<1	0
Subjects with ≥1 systemic reactogenicity event ^{†,¶}	25	1	<1	26	1	<1
Headache	13	<1	<1	14	1	<1
Fatigue	12	<1	0	12	<1	<1
Muscle Pain	9	<1	<1	9	<1	<1
Joint Pain	8	<1	0	8	<1	<1
Nausea	5	<1	0	5	<1	<1
Shivering / Chills	5	<1	0	4	<1	<1
Fever ^{#,P}	<1	<1	0	1	<1	0

NOTE: Data based on the most severe response reported by subjects. Results ≥1% reported to nearest whole percent; results >0 but <1% reported as <1%.

*Comparator = U.S.-licensed comparator quadrivalent inactivated influenza vaccine, Fluarix Quadrivalent, manufactured by GlaxoSmithKline.

†Study 2 is registered as NCT02285998 under the National Clinical Trials registry.

‡ Reactogenicity Populations were defined as all randomized subjects who received study vaccine according to the treatment actually received and who had at least one non-missing data point for injection site, systemic or body temperature reactogenicity categories. For local pain, tenderness, and systemic reactions: Grade 1=No interference with activity. Grade 2=Some interference with activity. Grade 3=Prevents daily activity. Grade 4=Required ER visit or hospitalization. For injection site redness and firmness/swelling: Grade 1=25 to ≤50 mm (small). Grade 2=51 to ≤100 mm (medium). Grade 3=>100 mm (large). Grade 4=necrosis or exfoliative dermatitis.

§Denominators for injection site reactions: Flublok Quadrivalent n = 4307, Comparator n = 4319.

¶Denominators for systemic reactions: Flublok Quadrivalent n = 4306, Comparator n = 4318.

#Denominators for fever: Flublok Quadrivalent n = 4262, Comparator n = 4282.

P Fever defined as ≥100.4°F (38°C). Grade 1 (≥100.4°F to ≤101.1°F); Grade 2 (101.2°F to ≤102.0°F); Grade 3 (102.1°F to ≤104°F). Grade 4 >104°F.

Among adults 18-49 years of age (Study 1), through 6 months post-vaccination, no deaths were reported. SAEs were reported by 12 subjects, 10 (1%) Flublok Quadrivalent recipients and 2 (0.6%) Comparator recipients. No SAEs were considered related to study vaccine.

Among adults 50 years of age and older (Study 2), 20 deaths occurred in the 6 months post-vaccination, including 8 Flublok Quadrivalent and 12 Comparator recipients. No deaths were considered related to study vaccine. SAEs were reported by 145 (3.4%) Flublok Quadrivalent recipients and 132 (3%) Comparator recipients. No SAEs were considered related to study vaccine.

In the 28 days following vaccination, one or more unsolicited treatment emergent adverse events occurred in 10.3% of Flublok Quadrivalent and 10.5% of Comparator recipients in Study 1 (adults 18-49 years of age) and in 13.9% of Flublok Quadrivalent and 14.1% of Comparator recipients in Study 2 (adults ≥50 years of age). In both studies, rates of individual events were similar between treatment groups, and most events were mild to moderate in severity.

Flublok (Trivalent Formulation)

The safety experience with Flublok is relevant to Flublok Quadrivalent because both vaccines are manufactured using the same process and have overlapping compositions [see *Description (11) in the full prescribing information*].

Flublok (trivalent formulation) has been administered to and safety data collected from a total of 4547 subjects in five clinical trials (Studies 3-7): 2497 adults 18 through 49 years, 972 adults 50 through 64 years, and 1078 adults 65 years and older. In Studies 3 - 5 and 7, SAEs were collected for 6 months post-vaccination. Study 6 collected SAEs through 30 days following receipt of vaccine. Study 6 also actively solicited pre-specified common hypersensitivity-type reactions through 30 days following receipt of vaccine as a primary endpoint.

Study 3 included 4648 subjects 18 through 49 years of age for safety analysis, randomized to receive Flublok (n=2344) or placebo (n=2304) [see *Clinical Studies (14) in the full prescribing information*].

Flublok[®] Quadrivalent (Influenza Vaccine), Sterile Solution for Intramuscular Injection 2022-2023 Formula

Study 4 included 602 subjects 50 through 64 years of age for safety analysis, randomized to receive Flublok (n=300) or another U.S.-licensed trivalent influenza vaccine (Fluzone[®], manufactured by Sanofi Pasteur, Inc.) as an active control (n=302).

Study 5 included 869 subjects aged 65 years and older for safety analysis, randomized to receive Flublok (n=436) or another U.S.-licensed trivalent influenza vaccine (Fluzone) as an active control (n=433).

Study 6 included 2627 subjects aged 50 years and older for safety analysis, randomized to receive Flublok (n=1314) or another U.S.-licensed trivalent influenza vaccine (Afluria, manufactured by Seqirus Pty Ltd.) as an active control (n=1313). Among subjects 50 through 64 years of age, 672 received Flublok and 665 received Afluria. Among subjects aged 65 years and older, 642 received Flublok and 648 received Afluria.

Study 7 was a Phase 2 dose-finding trial conducted in adults 18 through 49 years of age, 153 of whom received Flublok 135 mcg, the licensed trivalent formulation.

Serious Adverse Events

Among 2497 adults 18-49 years of age (Studies 3 and 7 pooled), through 6 months post-vaccination, two deaths were reported, one in a Flublok recipient and one in a placebo recipient. Both deaths occurred more than 28 days following vaccination and neither was considered vaccine-related. SAEs were reported by 32 Flublok recipients and 35 placebo recipients. One SAE (pleuropneumonitis) in a Flublok recipient was assessed as possibly related to the vaccine.

Among 972 adults 50-64 years of age (Studies 4 and 6 pooled), through up to 6 months post-vaccination, no deaths occurred, and SAEs were reported by 10 subjects, 6 Flublok recipients and 4 Comparator recipients. One of the SAEs, vasovagal syncope following injection of Flublok, was considered related to administration of study vaccine.

Among 1078 adults 65 years of age and older (Studies 5 and 6 pooled), through up to 6 months post-vaccination, 4 deaths occurred, 2 in Flublok recipients and 2 in Comparator recipients. None were considered related to the study vaccines. SAEs were reported by 80 subjects (37 Flublok recipients, 43 Comparator recipients). None were considered related to the study vaccines.

Among 1314 adults 50 years of age and older (Study 7) for whom the incidence of rash, urticaria, swelling, non-pitting edema, or other potential hypersensitivity reactions were actively solicited for 30 days following vaccination, a total of 2.4% of Flublok recipients and 1.6% of Comparator recipients reported such events over the 30 day follow-up period. A total of 1.9% and 0.9% of Flublok and Comparator recipients, respectively, reported these events in the 7 days following vaccination. Of these solicited events, rash was most frequently reported (Flublok 1.3%, Comparator 0.8%) over the 30 day follow-up period.

6.2 Postmarketing Experience

The following events have been spontaneously reported during post-approval use of Flublok Quadrivalent. They are described because of the temporal relationship, the biologic plausibility of a causal relationship to Flublok Quadrivalent, and their potential seriousness. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Immune system disorders: anaphylaxis, allergic reactions, and other forms of hypersensitivity (including urticaria).

7 DRUG INTERACTIONS

Data evaluating the concomitant administration of Flublok Quadrivalent with other vaccines are not available.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure

Pregnancy outcomes in women who have been exposed to Flublok Quadrivalent during pregnancy are being monitored. Sanofi Pasteur Inc. is maintaining a prospective pregnancy exposure registry to collect data on pregnancy outcomes and newborn health status following vaccination with Flublok Quadrivalent during pregnancy. Healthcare providers are encouraged to enroll women who receive Flublok Quadrivalent during pregnancy in Sanofi Pasteur Inc.'s vaccination pregnancy registry by calling 1-800-822-2463.

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively. Available data on Flublok Quadrivalent and Flublok (trivalent formulation) administered to pregnant women are insufficient to inform vaccine-associated risks in pregnant women.

There were no developmental studies of Flublok Quadrivalent formulation performed in animals. The developmental effects of Flublok (trivalent formulation) are relevant to Flublok Quadrivalent because both vaccines are manufactured using the same process and have overlapping compositions. A developmental study of Flublok (trivalent formulation) has been performed in rats administered 0.5 mL divided of Flublok (trivalent formulation) prior to mating and during gestation. This study revealed no evidence of harm to the fetus due to Flublok (trivalent formulation) [see *Data*].

Clinical Considerations

Disease-associated Maternal and/or Embryo/Fetal Risk

Pregnant women are at increased risk of complications associated with influenza infection compared to non-pregnant women. Pregnant women with influenza may

Flublok[®] Quadrivalent (Influenza Vaccine), Sterile Solution of Intramuscular Injection 2022-2023 Formula

be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.

Data

Animal

In a developmental toxicity study, female rats were administered 0.5 mL divided of Flublok (trivalent formulation) by intramuscular injection twice prior to mating (35 days and 14 days prior to mating) and on gestation Day 6. No vaccine-related fetal malformations or variations and no adverse effects on pre-weaning development were observed in the study.

8.2 Lactation

Risk Summary

It is not known whether Flublok Quadrivalent is excreted in human milk. Data are not available to assess the effects of Flublok (trivalent formulation) or Flublok 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 Flublok Quadrivalent and any potential adverse effects on the breastfed child from Flublok Quadrivalent or from the underlying maternal condition. For preventive vaccines, the underlying condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

Data from a randomized, controlled trial demonstrated that children 6 months to less than 3 years of age had diminished hemagglutinin inhibition (HI) responses to Flublok (trivalent formulation) as compared to a U.S.-licensed influenza vaccine approved for use in this population, strongly suggesting that Flublok (trivalent formulation) would not be effective in children younger than 3 years of age. Safety and effectiveness of Flublok Quadrivalent have not been established in children 3 years to less than 18 years of age.

8.5 Geriatric Use

Data from an efficacy study (Study 2), which included 1759 subjects ≥65 years and 525 subjects ≥75 years who received Flublok Quadrivalent, are insufficient to determine whether elderly subjects respond differently from younger subjects [see *Clinical Trials Experience (6.1) and Clinical Studies (14) in the full prescribing information*].

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Please continue reading to see Brief Summary of Prescribing Information for Fluzone High-Dose Quadrivalent (Influenza Vaccine).

Fluzone[®] High-Dose Quadrivalent (Influenza Vaccine), Suspension, for intramuscular injection 2022-2023 Formula

Rx Only

Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

Fluzone[®] High-Dose Quadrivalent is a vaccine indicated for active immunization for the prevention of influenza caused by influenza A subtype viruses and type B viruses contained in the vaccine.

Fluzone High-Dose Quadrivalent is indicated for use in persons 65 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular use only

2.1 Dose and Schedule

Fluzone High-Dose Quadrivalent should be administered as a single 0.7 mL injection by the intramuscular route in adults 65 years of age and older.

2.2 Administration

Inspect Fluzone High-Dose Quadrivalent visually for particulate matter and/or discoloration prior to administration. If either of these conditions exists the vaccine should not be administered.

Before administering a dose of vaccine, shake the prefilled syringe.

The preferred site for intramuscular injection is the deltoid muscle. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk.

Do not administer this product intravenously.

Fluzone High-Dose Quadrivalent should not be combined through reconstitution or mixed with any other vaccine.

4 CONTRAINDICATIONS

A severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine [see *Description (11) in the full prescribing information*], including egg protein, or to a previous dose of any influenza vaccine is a contraindication to administration of Fluzone High-Dose Quadrivalent.

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

If Guillain-Barré syndrome (GBS) has occurred within 6 weeks following any previous influenza vaccination, the decision to give Fluzone High-Dose 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 1 additional case per 1 million persons vaccinated. GBS has also been temporally associated with influenza disease. (See references 1 and 2.)

5.2 Preventing and Managing Allergic Reactions

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

5.3 Altered Immunocompetence

If Fluzone High-Dose Quadrivalent is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be lower than expected.

5.4 Limitations of Vaccine Effectiveness

Vaccination with Fluzone High-Dose Quadrivalent may not protect all recipients.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trial(s) of a vaccine cannot be directly compared to rates in the clinical trial(s) of another vaccine and may not reflect the rates observed in practice. One clinical study has evaluated the safety of Fluzone High-Dose Quadrivalent.

Study 1 (NCT03282240, see https://clinicaltrials.gov) was a randomized, active-controlled, modified double-blind pre-licensure trial conducted in the U.S. The study compared the safety and immunogenicity of Fluzone High-Dose Quadrivalent to those of Fluzone High-Dose (trivalent formulation). The safety analysis set included 1777 Fluzone High-Dose Quadrivalent recipients, 443 Fluzone High-Dose recipients, and 450 investigational Fluzone High-Dose containing the alternate B influenza strain recipients.

The most common reactions occurring after Fluzone High-Dose Quadrivalent administration were injection-site pain (41.3%), myalgia (22.7%), headache (14.4%), and malaise (13.2%). Onset usually occurred within the first 3 days after vaccination. The majority of solicited reactions resolved within three days of vaccination.

Table 1 displays solicited adverse reactions for Fluzone High-Dose Quadrivalent compared to Fluzone High-Dose reported within 7 days after vaccination and collected using standardized diary cards.

Table 1: Study 1: Frequency of Solicited Injection-Site Reactions and Systemic Adverse Events within 7 Days after Vaccination with Fluzone High-Dose Quadrivalent or Fluzone High-Dose, Adults 65 Years of Age and Older

**Fluzone® High-Dose Quadrivalent
(Influenza Vaccine), Suspension, for intramuscular injection
2022-2023 Formula**

	Fluzone High-Dose Quadrivalent (N [†] =1761-1768)		Fluzone High-Dose [‡] (N [†] =885-889)	
	Percentage		Percentage	
	Any	Grade 3	Any	Grade 3
Local Reactions				
Injection Site Pain [§]	41.3	0.7	36.4	0.2
Injection Site Erythema [¶]	6.2	0.6	5.7	0.2
Injection Site Swelling [¶]	4.9	0.3	4.7	0.1
Injection Site Induration [¶]	3.7	0.2	3.5	0.1
Injection Site Bruising [¶]	1.3	0.0	1.1	0.0
Systemic Reactions				
Myalgia [§]	22.7	0.9	18.9	0.7
Headache [§]	14.4	0.6	13.6	0.4
Malaise [§]	13.2	0.7	13.4	0.4
Shivering [§]	5.4	0.3	4.7	0.3
Fever [#]	0.4	0.2	0.9	0.2

*NCT03282240

†N is the number of vaccinated participants with available data for the events listed

‡Safety results for the Fluzone High-Dose and investigational Fluzone High-Dose containing the alternate B influenza strain recipients were pooled for the analysis.

§Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

¶Grade 3: > 100 mm

#Grade 3: ≥ 102.1°F (39.0°C)

Based on data from Fluzone High-Dose, solicited injection site reactions and systemic adverse reactions were slightly more frequent after vaccination with Fluzone High-Dose compared to a standard-dose vaccine.

Unsolicited non-serious adverse events were reported in 279 (15.7%) recipients in the Fluzone High-Dose Quadrivalent group and 140 (15.7%) recipients in the Fluzone High-Dose group. The most commonly reported unsolicited adverse event was cough.

Within 180 days post-vaccination, 80 (4.5%) Fluzone High-Dose Quadrivalent recipients and 48 (5.4%) Fluzone High-Dose recipients experienced a serious adverse event (SAE). None of the SAEs were assessed as related to the study vaccines.

6.2 Postmarketing Experience

The following additional adverse events have been spontaneously reported during the postmarketing use of Fluzone High-Dose, Fluzone, or Fluzone Quadrivalent and may occur in people receiving Fluzone High-Dose Quadrivalent. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. 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 Fluzone High-Dose, Fluzone, or Fluzone Quadrivalent.

- **Blood and Lymphatic System Disorders:** Thrombocytopenia, lymphadenopathy
- **Immune System Disorders:** Anaphylaxis, other allergic/hypersensitivity reactions (including urticaria, angioedema)
- **Eye Disorders:** Ocular hyperemia
- **Nervous System Disorders:** Guillain-Barré syndrome (GBS), convulsions, febrile convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination), dizziness, paresthesia
- **Vascular Disorders:** Vasculitis, vasodilatation
- **Respiratory, Thoracic and Mediastinal Disorders:** Dyspnea, cough, wheezing, throat tightness, oropharyngeal pain, and rhinorrhea
- **Gastrointestinal Disorders:** Vomiting
- **Skin and Subcutaneous Tissue Disorders:** Stevens-Johnson syndrome
- **General Disorders and Administration Site Conditions:** pruritus, asthenia/fatigue, chest pain, chills

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Fluzone High-Dose Quadrivalent is not approved for use in persons <65 years of age. There are limited human data on Fluzone High-Dose and no animal data available on Fluzone High-Dose Quadrivalent to establish whether there is a vaccine-associated risk with use of Fluzone High-Dose Quadrivalent in pregnancy.

8.2 Lactation

Fluzone High-Dose Quadrivalent is not approved for use in persons <65 years of age. No human or animal data are available to assess the effects of Fluzone High-Dose Quadrivalent on the breastfed infant or on milk production/excretion.

8.4 Pediatric Use

Safety and effectiveness of Fluzone High-Dose Quadrivalent in children younger than 18 years of age have not been established.

8.5 Geriatric Use

Safety, immunogenicity, and efficacy of Fluzone High-Dose Quadrivalent have been evaluated in adults 65 years of age and older [see *Adverse Reactions (6.1) and Clinical Studies (14) in the full prescribing information*].

Manufactured by:
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