FluQuadri™

Quadrivalent Influenza Vaccine

Types A and B subvirion

XXXX Formula

FULL PRESCRIBING INFORMATION:

INDICATIONS AND USAGE

FluQuadri™ is a quadrivalent influenza 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.

FluQuadri is approved for use in persons 6 months of age and older.

DOSAGE AND ADMINISTRATION

- **For intramuscular use only**

Dose and Schedule

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

Table 1: Dose and Schedule for FluQuadri

Age	Dose	Schedule
6 months through 8 years	One or two 0.5 mL doses[a]	If 2 doses, administer at least 1 month apart
9 years and older	One 0.5 mL dose	-

[a]1 or 2 doses depends on vaccination history and local or national recommendations

"-" indicates information is not applicable

Administration

Parenteral drug products should be inspected visually for particulate matter and/or discoloration prior to administration, whenever solution and container permit. If either of these conditions exist, the vaccine should not be administered.

Before administering a dose of vaccine, shake the vial. Withdraw the vaccine using a sterile needle and sterile syringe. Discard unused portion. Use a separate sterile needle and syringe for each dose withdrawn from the multi-dose vial. A maximum of ten doses can be withdrawn from the multi-dose vial.

The preferred sites for intramuscular injection are the anterolateral aspect of the thigh in infants 6 months through 11 months of age, the anterolateral aspect of the thigh (or the deltoid muscle if muscle mass is adequate) in persons 12 months through 35 months of age, or the deltoid muscle in persons ≥36 months of age. 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, intradermally, or subcutaneously.

FluQuadri vaccine should not be combined through reconstitution or mixed with any other vaccine.

DOSAGE FORMS AND STRENGTHS

FluQuadri is a suspension for injection.

FluQuadri is supplied in 1 presentation (see Table 1 for Dose and Schedule):

1) Multi-dose vial, 5 mL, for persons 6 months of age and older.

CONTRAINDICATIONS

Do not administer FluQuadri to anyone with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine [see DESCRIPTION], including egg protein, or to a previous dose of any influenza vaccine.

WARNINGS AND PRECAUTIONS

Guillain-Barré Syndrome

The 1976 swine influenza vaccine was associated with an elevated risk 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 1 additional case per 1 million persons vaccinated. (See ref. 1). If GBS has occurred within 6 weeks of previous influenza vaccination, the decision to give FluQuadri should be based on careful consideration of the potential benefits and risks.

Preventing and Managing Allergic Reactions

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

Altered Immunocompetence

If FluQuadri is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the expected immune response may not be obtained.

Limitations of Vaccine Effectiveness

Vaccination with FluQuadri may not protect all recipients.

Syncope

Syncope (fainting) has been reported following vaccination with FluQuadri. Procedures should be in place to avoid injury from fainting.

ADVERSE REACTIONS

Clinical Trials Experience

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

Children 6 Months through 8 Years of Age

In a multi-center study conducted in the US, children 6 months through 35 months of age received one or two 0.25 mL doses of either Fluzone® Quadrivalent[a] or one of two formulations of a comparator trivalent influenza vaccine (TIV-1 or TIV-2), and children 3 years through 8 years of age received one or two 0.5 mL doses of either Fluzone Quadrivalent, TIV-1, or TIV-2. Each of the trivalent formulations contained an influenza type B virus that corresponded to one of the two type B viruses in Fluzone Quadrivalent (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). For participants who received two doses, the doses were administered approximately 4 weeks apart. The safety analysis set included 1841 children 6 months through 35 months of age and 2506 children 3 years through 8 years of age.

[a] Fluzone® Quadrivalent is the tradename for FluQuadri in the US. Fluzone is a registered trademark of Sanofi Pasteur Inc.

In children 6 months through 35 months of age, the most common (≥10%) injection-site reactions were pain (57%)[a] or tenderness (54%)[b], erythema (37%), and swelling (22%); the most common solicited systemic adverse reactions were irritability (54%)[b], abnormal crying (41%)[b], malaise (38%)[a], drowsiness (38%)[b], appetite loss (32%)[b], myalgia (27%)[a], vomiting (15%)[b], and fever (14%). In children 3 years through 8 years of age, the most common (≥10%) injection-site reactions were pain (67%), erythema (34%), and swelling (25%); the most common solicited systemic adverse reactions were myalgia (39%), malaise (32%), and headache (23%).

During the 28 days following vaccination, a total of 16 (0.6%) recipients in the Fluzone Quadrivalent group, 4 (0.5%) recipients in the TIV-1 group, and 4 (0.6%) recipients in the TIV-2 group, experienced at least one SAE; no deaths occurred. Throughout the study period, a total of 41 (1.4%) recipients in the Fluzone Quadrivalent group, 7 (1.0%) recipients in the TIV-1 group, and 14 (1.9%) recipients in the TIV-2 group, experienced at least one SAE. Three SAEs were considered to be possibly related to vaccination: croup in a Fluzone Quadrivalent recipient and 2 episodes of febrile seizure, 1 each in a TIV-1 recipient and a TIV-2 recipient.

[a] Assessed in children 24 months through 35 months of age

[b] Assessed in children 6 months through 23 months of age

Adults

In a multi-center trial conducted in the US, adults 18 years of age and older received one dose of either Fluzone Quadrivalent or one of two formulations of comparator trivalent influenza vaccine (TIV-1 or TIV-2). Each of the trivalent formulations contained an influenza type B virus that corresponded to one of the two type B viruses in Fluzone Quadrivalent (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). The safety analysis set included 570 recipients, half aged 18-60 years and half aged 61 years or older.

In adults 18 years and older, the most common (≥10%) injection-site reaction was pain (47%); the most common solicited systemic adverse reactions were myalgia (24%), headache (16%), and malaise (11%). In the follow-up period, there were two SAEs, 1 (0.5%) in the Fluzone Quadrivalent group and 1 (0.5%) in the TIV-2 group.

Geriatric Adults

In a multi-center trial conducted in the US, adults 65 years of age and older received one dose of either Fluzone Quadrivalent, or one of two formulations of comparator trivalent influenza vaccine (TIV-1 or TIV-2). Each of the trivalent formulations contained an influenza type B virus that corresponded to one of the two type B viruses in Fluzone Quadrivalent (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). The safety analysis set included 675 recipients.

In adults 65 years of age and older, the most common (≥10%) injection-site reaction was pain (33%); the most common solicited systemic adverse reactions were myalgia (18%), headache

(13%), and malaise (11%). Three SAEs were reported during the follow-up period, 2 (0.9%) in the TIV-1 group and 1 (0.4%) in the TIV-2 group.

Reporting adverse reactions

Persons who receive the vaccine and their guardians should be instructed to report any adverse or unusual reaction to their healthcare provider.

Post-Marketing Experience

The following events have been spontaneously reported during the post-approval use of Fluzone (trivalent) or Fluzone 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 (trivalent) 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, vasodilation/flushing
- *Respiratory, Thoracic and Mediastinal Disorder*s: Dyspnea, pharyngitis, rhinitis, cough, wheezing, throat tightness, oropharyngeal pain, rhinorrhea.
- *Skin and Subcutaneous Tissue Disorders*: Rash, pruritus, and Stevens-Johnson syndrome
- *General Disorders and Administration Site Conditions*: Asthenia/fatigue, pain in extremities, chest pain
- *Gastrointestinal Disorders:* Vomiting

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

Pregnancy

According to WHO, vaccination is especially important for populations who are at a higher risk of serious influenza complications. Therefore, WHO recommends annual vaccination for pregnant women at any stage of pregnancy.

Pregnancy Exposure Registry

Sanofi Pasteur Inc. is maintaining a prospective pregnancy exposure registry to collect data on pregnancy outcomes and newborn health status following vaccination with Fluzone Quadrivalent during pregnancy. Healthcare providers are encouraged to enroll women who receive Fluzone

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 risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Available data with Fluzone Quadrivalent use in pregnant women are insufficient to inform vaccine-associated risk of adverse developmental outcomes.

A developmental and reproductive toxicity study was performed in female rabbits given a 0.5 mL/dose of Fluzone Quadrivalent prior to mating and during gestation (a single human dose is 0.5 mL). This study revealed no adverse effects to the fetus or pre-weaning development due to Fluzone Quadrivalent [see Animal Data (8.1)].

Data

Animal Data: In a developmental and reproductive toxicity study female rabbits were administered a 0.5 mL/dose of Fluzone Quadrivalent by intramuscular injection 24 and 10 days before insemination, and on Days 6, 12, and 27 of gestation (a single human dose is 0.5 mL). There were no adverse effects on pre-weaning development or vaccine-related fetal malformations noted in this study.

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 who contract influenza may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.

Lactation

Risk Summary

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

Pediatric Use

Safety and effectiveness of FluQuadri in children below the age of 6 months have not been established.

Geriatric Use

Safety and immunogenicity of FluQuadri were evaluated in adults 65 years of age and older. [See ADVERSE REACTIONS and CLINICAL STUDIES] Antibody responses to FluQuadri are lower in persons ≥65 years of age than in younger adults.

DESCRIPTION

FluQuadri (Quadrivalent Influenza Vaccine) for intramuscular injection is an inactivated influenza vaccine, prepared from influenza viruses propagated in embryonated chicken eggs. The virus-containing allantoic fluid is harvested and inactivated with formaldehyde. Influenza virus is concentrated and purified in a linear sucrose density gradient solution using a continuous flow centrifuge. The virus is then chemically disrupted using a non-ionic surfactant, octylphenol ethoxylate (Triton® X-100), producing a "split virus". The split virus is further purified and then suspended in sodium phosphate-buffered isotonic sodium chloride solution. The FluQuadri process uses an additional concentration factor after the ultrafiltration step in order to obtain a higher hemagglutinin (HA) antigen concentration. Antigens from the four strains included in the vaccine are produced separately and then combined to make the quadrivalent formulation.

FluQuadri suspension for injection is clear and slightly opalescent in color.

Antibiotics are not used in the manufacture of FluQuadri.

The FluQuadri multi-dose vial presentation is not made with natural rubber latex.

FluQuadri is standardized according to United States Public Health Service requirements and is formulated to contain 60 micrograms (mcg) HA per 0.5 mL dose in the recommended ratio of 15 mcg HA of each of the following four influenza strains recommended for the XXXX YYYYYY Hemisphere influenza season: A/XXXX (H1N1), A/XXXX (H3N2), B/XXXX (B Yamagata lineage), and B/XXXX (a B/XXXX, B Victoria lineage). The amounts of HA and other ingredients per dose of vaccine are listed in Table 2.

Table 2: FluQuadri Ingredients

Ingredient	**Quantity (per dose)**
	FluQuadri 0.5 mL Dose
Active Substance: Split influenza virus, inactivated strains[a]:	60 mcg HA total
A (H1N1)	15 mcg HA
A (H3N2)	15 mcg HA
B/(Victoria lineage)	15 mcg HA
B/(Yamagata lineage)	15 mcg HA
Other:	
Sodium phosphate-buffered isotonic sodium chloride solution	QS[b] to appropriate volume
Formaldehyde	≤100 mcg
Octylphenol ethoxylate	≤250 mcg
Preservative	
Thimerosal	25 mcg mercury

[a]per United States Public Health Service (USPHS) requirement
[b]Quantity Sufficient

CLINICAL PHARMACOLOGY

Mechanism of Action

Influenza illness and its complications follow infection with influenza viruses. Global surveillance of influenza identifies yearly antigenic variants. For example, since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation. Since 2001, two distinct lineages of influenza B (Victoria and Yamagata lineages) have co-circulated worldwide. Protection from influenza virus infection has not been correlated with a specific level of hemagglutination inhibition (HI) antibody titer post-vaccination. However, in some human studies, antibody titers ≥1:40 have been associated with protection from influenza illness in up to 50% of subjects.

Antibodies against one influenza virus type or subtype confer limited or no protection against another. Furthermore, antibodies 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 virologic basis for seasonal epidemics and the reason for the usual change of one or more new strains in each year's influenza vaccine. Therefore, influenza vaccines are standardized to contain the hemagglutinins of influenza virus strains representing the influenza viruses likely to be circulating in the next season.

Annual vaccination with the current vaccine is recommended because immunity during the year after vaccination declines and because circulating strains of influenza virus change from year to year.

NON-CLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

FluQuadri has not been evaluated for carcinogenic or mutagenic potential. A reproductive study of female rabbits vaccinated with FluQuadri was performed and revealed no evidence of impaired female fertility [see *Pregnancy*].

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CLINICAL STUDIES

Immunogenicity of Fluzone Quadrivalent in Children 6 Months through 8 Years of Age

In a multi-center study conducted in the US, 1419 children 6 months through 35 months of age and 2101 children 3 years through 8 years of age were included in the per-protocol immunogenicity analysis. Participants 6 months through 35 months of age received one or two 0.25 mL doses and participants 3 years through 8 years of age received or one or two 0.5 mL doses, respectively of Fluzone Quadrivalent, TIV-1, or TIV-2. For participants who received two doses, the doses were administered approximately 4 weeks apart.

HI antibody geometric mean titers (GMTs) and seroconversion rates 28 days following vaccination with Fluzone Quadrivalent were non-inferior to those following each TIV for all four strains, based on pre-specified criteria (the lower limit of the 2-sided 95% CI of the ratio of GMTs [Fluzone Quadrivalent divided by pooled TIV for the A strains, or the TIV containing the corresponding B strain] was >0.66 and the lower limit of the 2-sided 95% CI of the difference in seroconversion rates [Fluzone Quadrivalent minus pooled TIV for the A strains, or the TIV containing the corresponding B strain] was >-10%). For strain A (H1N1), the GMT ratio was 1.03 (95% CI: 0.93; 1.14) and the difference of seroconversion rates was 0.9% (95% CI: -0.9%; 3.0%).

For strain A (H3N2), the GMT ratio was 0.99 (95% CI: 0.91; 1.08) and the difference of seroconversion rates was 3.8% (95% CI: 1.4%; 6.3%). For strain B/Brisbane/60/2008 (B Victoria), the GMT ratio was 1.34 (95% CI: 1.20; 1.50) and the difference of seroconversion rates was 10.7% (95% CI: 6.4%; 15.1%). For strain B/Florida/04/2006 (B Yamagata), the GMT ratio was 1.06 (95% CI: 0.94; 1.18) and the difference of seroconversion rates was 2.0% (95% CI: -2.2%; 6.4%). Non-inferiority immunogenicity criteria based on HI antibody GMTs and seroconversion rates were also met when age subgroups (6 months to <36 months and 3 years to <9 years) were examined.

In addition, HI antibody GMTs and seroconversion rates following Fluzone Quadrivalent were higher than those following TIV for the B strain not contained in each respective TIV based on pre-specified criteria (the lower limit of the 2-sided 95% CI of the ratio of the GMTs [Fluzone Quadrivalent divided by TIV] >1.5 for each B strain in Fluzone Quadrivalent compared with the corresponding B strain not contained in each TIV and the lower limit of the two 2-sided 95% CI of the difference of the seroconversion rates [Fluzone Quadrivalent minus TIV] >10% for each B strain in Fluzone Quadrivalent compared with the corresponding B strain not contained in each TIV).

Immunogenicity of the 0.5 mL Dose of Fluzone Quadrivalent in Children 6 Months through 35 Months of Age

In a multi-center safety and immunogenicity study conducted in the US, 1027 children, 6 months through 35 months of age, were included in the per-protocol immunogenicity analysis. The

distribution of demographic characteristics was similar to that of the safety analysis set [see Adverse Reactions (6.1)].

In this study, children 6 months through 35 months of age received one or two doses of either 0.25 mL or 0.5 mL of Fluzone Quadrivalent. Non-inferiority of the 0.5 mL dose(s) relative to the 0.25 mL dose(s) of Fluzone Quadrivalent was demonstrated for all four strains based on pre-specified criteria (lower limit of the 2-sided 95% CI of the ratio of GMTs between groups >0.667; lower limit of the 2-sided 95% CI of the difference in seroconversion rates >-10%). GMT ratios (GMT0.5-mL dose divided by GMT0.25-mL dose) for the A/H1N1, A/H3N2, B Victoria lineage, and B Yamagata lineage strains were 1.42 (95% CI: 1.16; 1.74), 1.48 (95% CI: 1.21; 1.82), 1.33 (95% CI: 1.09; 1.62), and 1.41 (95% CI: 1.17; 1.70), respectively. Seroconversion rate (SCR) differences ($SCR_{0.5\text{-mL dose}}$ minus $SCR_{0.25\text{-mL dose}}$) for the A/H1N1, A/H3N2, B Victoria lineage, and B Yamagata lineage strains were 4.6% (95% CI: -0.4%; 9.6%), 5.1% (95% CI: 0.4%; 9.8%), 1.3% (95% CI: -2.9%; 5.6%), and 2.6% (95% CI: -1.4%; 6.5%).

Immunogenicity of Fluzone Quadrivalent in Adults ≥18 Years of Age

In a multi-center study conducted in the US, 565 adults 18 years of age and older who had received one dose of Fluzone Quadrivalent, TIV-1, or TIV-2 were included in the per-protocol immunogenicity analysis.

HI antibody GMTs 21 days following vaccination with Fluzone Quadrivalent were non-inferior to those following each TIV for all four strains, based on pre-specified criteria (the lower limit of the

2-sided 95% CI of the ratio of GMTs [Fluzone Quadrivalent divided by pooled TIV for the A strains, or the TIV containing the corresponding B strain] was >2/3). For strain A (H1N1), the GMT ratio was 1.06 (95% CI: 0.87; 1.31), for strain A (H3N2), the GMT ratio was 0.90 (95% CI: 0.70; 1.15), for strain B/Brisbane/60/2008 (B Victoria), the GMT ratio was 0.89 (95% CI: 0.70; 1.12), and for strain B/Florida/04/2006 (B Yamagata), the GMT ratio was 1.15 (95% CI: 0.93; 1.42).

Immunogenicity of Fluzone Quadrivalent in Geriatric Adults ≥65 Years of Age

In a multi-center study conducted in the US, 660 adults 65 years of age and older were included in the per-protocol immunogenicity analysis.

HI antibody GMTs 21 days following vaccination with Fluzone Quadrivalent were non-inferior to those following TIV for all four strains, based on pre-specified criteria (the lower limit of the 2-sided 95% CI of the ratio of GMTs [Fluzone Quadrivalent divided by pooled TIV for the A strains, or the TIV containing the corresponding B strain] was >0.66). For strain A (H1N1), the GMT ratio was 0.85 (95% CI: 0.67; 1.09), for strain A (H3N2), the GMT ratio was 1.55 (95% CI: 1.25; 1.92), for strain B/Brisbane/60/2008 (B Victoria), the GMT ratio was 1.27 (95% CI: 1.05; 1.55), and for strain B/Florida/04/2006 (B Yamagata), the GMT ratio was 1.11 (95% CI: 0.90; 1.37). Seroconversion rates 21 days following Fluzone Quadrivalent were non-inferior to those following TIV for H3N2, B/Brisbane, and B/Florida, but not for H1N1, based on pre-specified criteria (the lower limit of the 2-sided 95% CI of the difference in seroconversion rates [Fluzone Quadrivalent minus pooled TIV for the A strains, or the TIV containing the corresponding B strain] was >-10%). For strain A (H1N1), the difference of seroconversion rates was -3.86% (95%

CI: -11.50%; 3.56%), for strain A (H3N2), the difference of seroconversion rates was 9.77% (95% CI: 1.96%; 17.20%), for strain B/Brisbane/60/2008 (B Victoria), the difference of seroconversion rates was 9.91% (95% CI: 1.96%; 17.70%), and for strain B/Florida/04/2006 (B Yamagata), the difference of seroconversion rates was 1.96% (95% CI: -6.73%; 10.60%).

The HI antibody GMT following Fluzone Quadrivalent was higher than that following TIV-1 for B/Florida but not higher than that following TIV-2 for B/Brisbane, based on pre-specified criteria (the lower limit of the 2-sided 95% CI of the ratio of the GMTs [Fluzone Quadrivalent divided by TIV] >1.5 for each B strain in Fluzone Quadrivalent compared with the corresponding B strain not contained in each TIV). The GMT ratio for B/Brisbane was 1.75 (95% CI: 1.43; 2.14). Seroconversion rates following Fluzone Quadrivalent were higher than those following TIV for the B strain not contained in each respective TIV, based on pre-specified criteria (the lower limit of the two 2-sided 95% CI of the difference of the seroconversion rates [Fluzone Quadrivalent minus TIV] >10% for each B strain in Fluzone Quadrivalent compared with the corresponding B strain not contained in each TIV).

HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Multi-dose vial, 5 mL, package of 1 (not made with natural rubber latex).

Storage and Handling

Store all FluQuadri presentations refrigerated at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Discard if vaccine has been frozen.

Do not use after the expiration date shown on the label.

FluQuadri is a trademark of Sanofi Pasteur Inc.

Manufactured by:

Sanofi Pasteur Inc.

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