

FluQuadri™

Quadrivalent Influenza Vaccine

Types A and B Subviron

2018 - 2019 Formula

FULL PRESCRIBING INFORMATION:

INDICATIONS AND USAGE

FluQuadri™ (Quadrivalent Influenza Vaccine) is an inactivated quadrivalent influenza vaccine indicated for active immunization for the prevention of influenza disease caused by influenza types A and 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 35 months	One or two doses ^a , 0.25 mL each	If 2 doses, administer at least 1 month apart

36 months through 8 years	One or two doses ^a , 0.5 mL each	If 2 doses, administer at least 1 month apart
9 years and older	One dose, 0.5 mL	-

^aPreviously unvaccinated children 6 months to < 9 years of age require two doses of seasonal influenza vaccine. Eligible children who have properly received one or more doses of seasonal influenza vaccine in the past are recommended to receive one dose per season thereafter.

"-" indicates information is not applicable

Administration

Inspect FluQuadri visually for particulate matter and/or discoloration prior to administration. If either of these conditions exist, the vaccine should not be administered.

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

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 \geq 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 2 presentations (see [Table 1](#) for Dose and Schedule):

1) Prefilled single-dose syringe (pink syringe plunger rod), 0.25 mL, for persons 6 months through 35 months of age.

2) Prefilled single-dose syringe (clear syringe plunger rod), 0.5 mL, for persons 36 months of age and older.

CONTRAINDICATIONS

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 is a contraindication to administration of FluQuadri.

Vaccination should be postponed in case of moderate or severe acute or febrile disease with or without fever but a mild disease with low-grade fever is usually not a reason to postpone vaccination.

WARNINGS AND PRECAUTIONS

Guillain-Barré Syndrome

Recurrence of Guillain-Barré syndrome (GBS) has been temporally associated with administration of influenza vaccine. 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.

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

Among children 6 months through 8 years of age, unsolicited non-serious adverse events were reported in 1360 (47.0%) recipients in the FluQuadri group, 352 (48.0%) recipients in the TIV-1 group, and 346 (48.0%) recipients in the TIV-2 group. The most commonly reported unsolicited non-serious adverse events were cough, vomiting, and pyrexia.

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 FluQuadri 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 FluQuadri, 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 FluQuadri (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.

In children 6 months through 35 months of age, the most common ($\geq 10\%$) injection-site reactions were pain (57.0%)^a or tenderness (54.1%)^b, erythema (37.3%), and swelling (21.6%); the most common solicited systemic adverse reactions were irritability (54.0%)^b, abnormal crying (41.2%)^b, malaise (38.1%)^a, drowsiness (37.7%)^b, appetite loss (32.3%)^b, myalgia (26.7%)^a, vomiting (14.8%)^b, and fever (14.3%). In children 3 years through 8 years of age, the most common ($\geq 10\%$) injection-site reactions were pain (66.6%), erythema (34.1%), and swelling (24.8%); the most common solicited systemic adverse reactions were myalgia (38.6%), malaise (31.9%), and headache (23.1%).

During the 28 days following vaccination, a total of 16 (0.6%) recipients in the FluQuadri 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

^a Assessed in children 24 months through 35 months of age

^b Assessed in children 6 months through 23 months of age

in the FluQuadri 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 FluQuadri recipient and 2 episodes of febrile seizure, 1 each in a TIV-1 recipient and a TIV-2 recipient. One death occurred in the TIV-1 group (a drowning 43 days post-vaccination).

Adults

Unsolicited non-serious adverse events were reported in 33 (17.4%) recipients in the FluQuadri group, 45 (23.7%) recipients in the TIV-1 group, and 45 (23.7%) recipients in the TIV-2 group. The most commonly reported unsolicited non-serious adverse events were headache, cough, and oropharyngeal pain.

In a multi-center trial conducted in the US, adults 18 years of age and older received one dose of either FluQuadri 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 FluQuadri (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 ($\geq 10\%$) injection-site reaction was pain (47.4%); the most common solicited systemic adverse reactions were myalgia (23.7%), headache (15.8%), and malaise (10.5%).

In the follow-up period, there were two SAEs, 1 (0.5%) in the FluQuadri group and 1 (0.5%) in the TIV-2 group. No deaths were reported during the trial period.

Geriatric Adults

Unsolicited non-serious adverse events were reported in 28 (12.4%) recipients in the FluQuadri group, 22 (9.8%) recipients in the TIV-1 group, and 22 (9.8%) recipients in the TIV-2 group. The most commonly reported adverse events were oropharyngeal pain, rhinorrhea, injection-site induration, and headache.

In a multi-center trial conducted in the US, adults 65 years of age and older received one dose of either FluQuadri, 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 FluQuadri (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 ($\geq 10\%$) injection-site reaction was pain (32.6%); the most common solicited systemic adverse reactions were myalgia (18.3%), headache (13.4%), and malaise (10.7%).

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. No deaths were reported during the trial period.

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

Currently, there are no post-marketing data available for FluQuadri vaccine.

The following events have been spontaneously reported during the post-approval use of the trivalent formulation of Fluzone. 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.

- *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 Disorders:* Dyspnea, pharyngitis, rhinitis, cough, wheezing, throat tightness
- *Skin and Subcutaneous Tissue Disorders:* Stevens-Johnson syndrome
- *General Disorders and Administration Site Conditions:* Pruritus, 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.

FluQuadri should not be mixed with any other vaccine in the same syringe.

If FluQuadri is to be given at the same time as another injectable vaccine(s), the vaccine(s) should always be administered at different injection sites.

Although inhibition of hepatic clearance of phenytoin, theophylline and warfarin has been reported after influenza vaccination, subsequent studies have not shown any evidence of undesirable effects related to this phenomenon.

If the vaccine is used in individuals deficient in producing antibodies due to immunosuppressive therapy, the expected immune response may not be obtained.

Effect on Laboratory Tests

Interference of FluQuadri with laboratory and/or diagnostic tests has not been studied. Following influenza vaccination, false positive results in serology tests using the ELISA method to detect antibodies against HIV1, hepatitis C, and especially HTLV1 have been observed. An appropriate

Western Blot test should be used to confirm or disprove the results of the ELISA test. The transient false-positive reactions could be due to a non-specific IgM response induced by the vaccine.

USE IN SPECIFIC POPULATIONS

Pregnancy

Animal reproduction studies have not been conducted with FluQuadri. It is also not known whether FluQuadri can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. FluQuadri should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether FluQuadri is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FluQuadri is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of FluQuadri in children below the age of 6 months have not been established. Safety and immunogenicity of FluQuadri was evaluated in children 6 months through 8 years of age. [See [ADVERSE REACTIONS](#) and [CLINICAL STUDIES](#).]

Geriatric Use

Safety and immunogenicity of FluQuadri was evaluated in adults 65 years of age and older. [See **ADVERSE REACTIONS** and **CLINICAL STUDIES**.] Antibody responses to FluQuadri are lower in persons \geq 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.

Neither antibiotics nor preservative are used in the manufacture of FluQuadri.

The FluQuadri prefilled syringe presentations are 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 2018 – 2019 Northern Hemisphere influenza season: A/Michigan/45/2015 X-275 (H1N1), A/Singapore/INFIMH-16-0019/2016 IVR-186 (H3N2), B/Phuket/3073/2013 (B Yamagata lineage), and B/Maryland/15/2016 BX-69A (a B/Colorado/6/2017-like virus, 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 0.25 mL Dose	FluQuadri 0.5 mL Dose
Active Substance: Split influenza virus, inactivated strains^a:	30 mcg HA total	60 mcg HA total
A (H1N1)	7.5 mcg HA	15 mcg HA
A (H3N2)	7.5 mcg HA	15 mcg HA
B/(Victoria lineage)	7.5 mcg HA	15 mcg HA
B/(Yamagata lineage)	7.5 mcg HA	15 mcg HA
Other:		
Sodium phosphate-buffered isotonic sodium chloride solution	QS ^b to appropriate volume	QS ^b to appropriate volume
Formaldehyde	≤ 50 mcg	≤ 100 mcg
Octylphenol ethoxylate	≤ 125 mcg	≤ 250 mcg
Preservative	None	None

^aper United States Public Health Service (USPHS) requirement

^bQuantity 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 $\geq 1:40$ 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 or for impairment of fertility.

CLINICAL STUDIES

Immunogenicity of FluQuadri 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 received one or two 0.25 mL doses or one or two 0.5 mL doses, respectively of FluQuadri, 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 FluQuadri 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 [FluQuadri 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 [FluQuadri 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 FluQuadri 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 [FluQuadri divided by TIV] > 1.5 for each B strain in FluQuadri 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 [FluQuadri minus TIV] > 10% for each B strain in FluQuadri compared with the corresponding B strain not contained in each TIV).

Immunogenicity of FluQuadri 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 FluQuadri, TIV-1, or TIV-2 were included in the per-protocol immunogenicity analysis.

HI antibody GMTs 21 days following vaccination with FluQuadri 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 [FluQuadri 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 FluQuadri in Geriatric Adults \geq 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 FluQuadri 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 [FluQuadri 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 FluQuadri 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 [FluQuadri 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 FluQuadri 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 [FluQuadri divided by TIV] >1.5 for each B strain in FluQuadri 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 FluQuadri 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 [FluQuadri minus TIV] > 10% for each B strain in FluQuadri compared with the corresponding B strain not contained in each TIV).

HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Single-dose, prefilled syringe (pink plunger rod), without needle, 0.25 mL, package of 5 (not made with natural rubber latex).

Single-dose, prefilled syringe (clear plunger rod), without needle, 0.5 mL, package of 5 (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.

Swiftwater PA 18370 USA

SANOFI PASTEUR 