For the use of a Registered Medical Practitioner or a Hospital or a Laboratory

QUADRIVALENT INACTIVATED INFLUENZA VACCINE (SPLIT VIRION) I.P.
SH-2022

FluQuadri®
FOR INTRAMUSCULAR INJECTION

INDICATIONS AND USAGE

FluQuadri® is an inactivated quadrivalent influenza vaccine indicated 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

Table 1: Dose and Schedule for FluQuadri®:

Age	Dose	Schedule
6 months through 35 months	One or two doses[a] , 0.5ml each	If 2 doses, administer at least 4 weeks apart
36 months through 8 years	One or two doses[a], 0.5 mL each	If 2 doses, administer at least 4 weeks apart
9 years and older	One dose, 0.5 mL	-

[a] 1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines

"-" 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 ≥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.

Prefilled single-dose syringe (clear syringe plunger rod), 0.5 mL, for persons 6 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®.

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

In a multi-center trial conducted in the US (Study 1), 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, receiving a 0.25-mL dose of FluQuadri® in Study 1 (NCT01240746, see http://clinicaltrials.gov), the most common (≥10%) injection-site reactions were pain (57%)[a] or tenderness (54.1%)[b], erythema (37.3%), and swelling (21.6%); the most common solicited systemic adverse reactions were irritability (54%)[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 (≥10%) injection-site reactions were pain (66.7%), 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%).

[a] Assessed in children 24 months through 35 months of age
[b] Assessed in children 6 months through 23 months of age

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.

0.5-mL Dose of FluQuadri® in Children 6 Months through 35 Months of Age
Study 2 (NCT02915302 see http://clinicaltrials.gov) was a randomized, observer-blinded, 2-arm, multi-center safety and immunogenicity study conducted in the US. In this study, 1950 children 6 months through 35 months of age were randomly assigned to receive FluQuadri® administered in either a volume of 0.25 mL (Group 1) or 0.5 mL (Group 2). For participants recommended to receive two doses of influenza vaccine as per Advisory Committee on Immunization Practices guidance, the same dose was administered 4 weeks after the first. The safety analysis set included 1941 participants who received at least 1 dose of study vaccine

Table below summarizes solicited injection-site and systemic adverse reactions reported within 7 days post-vaccination via diary cards for the 0.25 mL and 0.5 mL volumes of FluQuadri® in children 6 months through 35 months of age.

Study 2[a]: Percentage of Solicited Injection-site and Systemic Adverse Reactions Within 7 Days After Vaccination in Children 6 Months Through 35 Month of Age (Safety Analysis Set)[b]

	FluQuadri® 0.25 mL[c] (N[d]=949)		**FluQuadri® 0.5 mL[c] (N[d]=992)**	
	Any (%)	**Grade 3[e] (%)**	**Any (%)**	**Grade 3[e] (%)**
Injection-site adverse reactions				
Tenderness	**47.3**	**1.7**	**50.4**	**1.2**
Redness	**23.1**	**0.0**	**24.3**	**0.2**
Swelling	**12.9**	**0.1**	**14.7**	**0.0**
Systemic adverse reactions				
Irritability	**47.4**	**3.6**	**48.6**	**4.0**

Abnormal Crying	**33.3**	**3.1**	**34.1**	**2.6**
Drowsiness	**31.9**	**2.1**	**31.3**	**1.6**
Loss of Appetite	**27.3**	**1.4**	**28.3**	**2.2**
Fever (≥100.4°F)[f]	**11.3**	**0.6**	**12.2**	**1.2**
Vomiting	**10.0**	**0.4**	**10.2**	**0.5**

[a] NCT02915302
[b] The safety analysis set includes all persons who received at least one dose of study vaccine
[c] Participants received 1 or 2 doses according to ACIP recommendations
[d] N is the number of participants in the safety analysis set
[e] Grade 3 - Injection-site tenderness: Cries when injected limb is moved, or the movement of the injected limb is reduced; Injection-site redness, Injection-site swelling: ≥ 50 mm; Irritability: inconsolable; Abnormal Crying: > 3 hours; Drowsiness: sleeping most of the time or difficult to wake up; Loss of Appetite: refuses ≥ 3 feeds/meals or refuses most feeds/meals; Fever: >103.1°F; Vomiting: ≥ 6 episodes per 24 hours or requiring parenteral hydration
[f] Fever measured by any route

The difference in fever rate (Group 2 minus Group 1) was 0.84% (95% CI: -2.13%; 3.80%), meeting the prespecified non-inferiority criterion (upper limit of the 2-sided 95% CI of the difference in fever rates < 5%). Participants were monitored for unsolicited adverse events and SAEs during the 28 days following vaccination. Unsolicited non-serious adverse events were reported in 417 (44%) participants in Group 1 and 394 (40%) participants in Group 2. The most commonly reported unsolicited non-serious adverse events in both groups were cough and rhinorrhea. Ten SAEs were reported during the 28-day follow-up period: 5 (0.5%) in Group 1 and 5 (0.5%) in Group 2.

Adults
In a multi-center trial conducted in the US (Study 3), 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 (≥ 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.

Geriatric Adults
In a multi-center trial conducted in the US (Study 4), 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 (≥ 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.

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.

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.

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 ≥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 presentation is not made with natural rubber latex.

FluQuadri® is standardized according to United States Public Health Service requirements and is formulated to contain the following four influenza strains recommended for the 2022 Southern Hemisphere influenza season: A/Victoria/2570/2019, IVR-215 (H1N1), A/Darwin/9/2021, SAN-010 (H3N2), B/Michigan/01/2021, wild type (a B/Austria/1359417/2021-like strain, B Victoria lineage) and B/Phuket/3073/2013, wild type (B Yamagata lineage). The single-dose, pre-filled syringe (0.5 mL) are manufactured and formulated without thimerosal or any other preservative. The amounts of HA and other ingredients per dose of vaccine are listed in Table 3.

Table 3: FluQuadri® Ingredients

Ingredient	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
Inactive ingredients	
Sodium chloride	6.6 g/L
Sodium phosphate dibasic anhydrous	3.830 g/L
Sodium phosphate monobasic anhydrous	0.410 g/L
Formaldehyde	≤100 mcg
Octylphenol ethoxylate (Triton® X-100)	≤250 mcg

[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 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 6 months through 35 months of age received one or two 0.25 mL doses -and participants 3 years though 8 years of age received one or two 0.5 mL doses, - 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 (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 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%.

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

In Study, 1027 children, 6 months through 35 months of age, were included in the per-protocol immunogenicity analysis. 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 FluQuari®. Non-inferiority of the 0.5 mL dose(s) relative to the 0.25 mL dose(s) of FluQuadri® 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 (SCR0.5-mL dose minus SCR0.25-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 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 ≥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 prespecified 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 (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.

The shelf life of FluQuadri® is 12 months.

INFORMATION FOR PATIENTS

Prior to administration of FluQuadri® vaccine, the healthcare professional should inform the patient of the potential benefits and risks to the patient (see **ADVERSE REACTIONS** and **WARNINGS AND**

PRECAUTIONS). Patients, parents or guardians should be instructed to report any **suspected adverse reactions to their healthcare professional who should report these events to** Sanofi Healthcare India Private Limited.

FluQuadri® is a trademark of Sanofi Pasteur Inc.

Manufactured by:
Sanofi Pasteur Inc.
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Imported and marketed by:
Sanofi Healthcare India Private Limited
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Registered Medical Practitioners can refer to the company website www.sanofi.in for the latest prescribing information

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