Efluelda
Influenza Vaccine
2023-2024 Formula
NORTHERN HEMISPHERE

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Efluelda is a vaccine indicated for active immunization for the prevention of influenza and the associated complication of pneumonia-related hospitalization.

Efluelda 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

Efluelda 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 Efluelda 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.

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

3 DOSAGE FORMS AND STRENGTHS

Efluelda is a suspension for injection.

Efluelda is supplied in prefilled syringes, 0.7 mL, for adults 65 years of age and older.

4 CONTRAINDICATIONS

A severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine *[see Description (11)]*, including egg protein, or to a previous dose of any influenza vaccine is a contraindication to administration of Efluelda.

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 Efluelda 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 Efluelda 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 Efluelda 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 Efluelda.

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 Efluelda to those of Fluzone High-Dose (trivalent formulation). The safety analysis set included 1777 Efluelda 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 Efluelda 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 Efluelda compared to Fluzone High-Dose reported within 7 days after vaccination and collected using standardized diary cards.

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

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

[a] NCT03282240
[b] N is the number of vaccinated participants with available data for the events listed
[c] Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
[d] Grade 3: > 100 mm
[e] Grade 3: ≥ 102.1°F (39.0°C)
[f] Safety results for the Fluzone High-Dose and investigational Fluzone High-Dose containing the alternate B influenza strain recipients were pooled for the analysis.

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 Efluelda 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%) Efluelda 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 Efluelda. 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

Efluelda 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 Efluelda to establish whether there is a vaccine-associated risk with use of Efluelda in pregnancy.

8.2 Lactation

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

8.4 Pediatric Use

Safety and effectiveness of Efluelda in children younger than 18 years of age have not been established.

8.5 Geriatric Use

Safety, immunogenicity, and efficacy of Efluelda have been evaluated in adults 65 years of age and older *[see Adverse Reactions (6.1) and Clinical Studies (14)].*

11 DESCRIPTION

Efluelda 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 Efluelda process uses an additional concentration factor after the ultrafiltration step in order to obtain a higher hemagglutinin (HA) antigen concentration.

Efluelda suspension for injection is a colorless opalescent liquid.

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

The Efluelda prefilled syringe presentation is not made with natural rubber latex.

Efluelda is standardized according to United States Public Health Service requirements and is formulated to contain HA of each of the following four influenza strains recommended for the 2023-2024 influenza season: A/Victoria/4897/2022 (H1N1)pdm09 - like strain (A/Victoria/4897/2022, IVR-238), A/Darwin/9/2021 (H3N2) - like strain (A/Darwin/9/2021, SAN-010), B/Austria/1359417/2021 - like strain (B/Michigan/01/2021, wild type), and B/Phuket/3073/2013 - like strain (B/Phuket/3073/2013, wild type). The amounts of HA and other ingredients per dose of vaccine are listed in Table 2.

Table 2: Efluelda Ingredients

Ingredient	**Quantity (per dose)**
	Efluelda 0.7 mL Dose
Active Substance: Split influenza virus, inactivated strains[a]:	240 mcg HA total
A (H1N1)	60 mcg HA
A (H3N2)	60 mcg HA
B (Victoria Lineage)	60 mcg HA
B (Yamagata Lineage)	60 mcg HA
Other:	
Sodium phosphate-buffered isotonic sodium chloride solution	QS[b] to appropriate volume
Formaldehyde	≤140 mcg
Octylphenol ethoxylate	≤350 mcg
Gelatin	None
Preservative	None

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Influenza illness and its complications may follow influenza infection. Global surveillance of influenza viruses identifies yearly antigenic variants. Since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation. Specific levels of hemagglutination inhibition (HI) antibody titer post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza virus infection. In some human studies, antibody titers ≥1:40 have been associated with protection from influenza illness in up to 50% of participants. (See references 3 and 4.)

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 U.S. during the influenza season.

Efluelda stimulates the immune system to produce antibodies that help prevent influenza disease.

13 NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Efluelda has not been evaluated for carcinogenic or mutagenic potential or for impairment of fertility.

14 CLINICAL STUDIES

14.1 Immunogenicity of Efluelda in Adults 65 Years of Age and Older

Study 1 (NCT03282240, see http://clinicaltrials.gov) was a randomized, active-controlled, modified double-blind trial in adults 65 years of age and older conducted in the US. The study compared the safety and immunogenicity of Efluelda to those of Fluzone High-Dose. The objective was to demonstrate immunologic non-inferiority of Efluelda to Fluzone High-Dose, as assessed by HAI geometric mean antibody titers (GMTs) at Day 28 and seroconversion rates, to strains common to formulations of both vaccines, based on pre-specified criteria.

A total of 2670 adults from 65 years of age were randomized (4:1:1) to receive one dose of either Efluelda or one of two formulations of Fluzone High-Dose (one formulation contained a B strain of the Victoria lineage [TIV-HD1] while the other contained a B strain of the Yamagata lineage [TIV-HD2]).

Females accounted for 58.2% of participants in the Efluelda group and 57.4% of participants in the Fluzone High-Dose group (TIV-HD1 and TIV-HD2, pooled). The mean age was 72.9 years

(range: 65 through 100 years) in the Efluelda group and the mean age was 73.0 (range: 65 through 95 years) in the Fluzone High-Dose group. The percentage of subjects 75 years of age or older was 35.4% in the Efluelda group and 35.8% in the Fluzone High-Dose group. Most participants were White (91.2% and 89.7%), followed by Black (6.8% and 8.0%), and Hispanic (2.8% and 2.6%) in the Efluelda and Fluzone High-Dose groups, respectively.

The immunogenicity results of Study 1 are summarized in Table 3 and Table 4 below.

Table 3: Study 1[a]: Post-vaccination HAI Antibody GMTs and Analyses of Non-inferiority of Efluelda Relative to Fluzone High-Dose, Adults 65 Years of Age and Older, Per-Protocol Analysis Set

Influenza Strain	GMT			GMT Ratio	Met Predefined Non-inferiority Criteria[e]
	QIV-HD N[b]=1679-1680	TIV-HD1[c] (B1 Victoria) N[b]=423	TIV-HD2[d] (B2 Yamagata) N[b]=430	QIV-HD over TIV-HD (95% CI)	
A (H1N1)[f]	312	374		0.83 (0.744; 0.932)	Yes
A (H3N2)[f]	563	594		0.95 (0.842; 1.066)	Yes
B1 (Victoria)	516	476	--	1.08 (0.958; 1.224)	Yes
B2 (Yamagata)	578	--	580	1.00 (0.881; 1.129)	Yes

[a] NCT03282240
[b] N is the number of vaccinated participants with available data for the immunologic endpoint listed
[c] TIV-HD1 contained A/Michigan/45/2015 (H1N1), A/Hong Kong/4801/2014 (H3N2), and B/Brisbane/60/2008 (B1, Victoria lineage)
[d] TIV-HD2 contained A/Michigan/45/2015 (H1N1), A/Hong Kong/4801/2014 (H3N2), and B/Phuket/3073/2013 (B2, Yamagata lineage)
[e] Predefined noninferiority criterion for the GMT ratio: the lower limit of the 95% CI of the GMT ratio (QIV-HD divided by TIV-HD) is >0.667
[f] Pooled TIV-HD group includes subjects vaccinated with either TIV-HD1 or TIV-HD2 for the A strain comparison

Table 4: Study 1[a]: Seroconversion Rates and Analyses of Non-inferiority of Efluelda Relative to Fluzone High-Dose, Adults 65 Years of Age and Older, Per-Protocol Analysis Set

Influenza Strain	Seroconversion Rates (Percentage)[b]	Difference of Seroconversion Rates	Met Predefined Non-inferiority Criteria[f]

	QIV-HD N[c]=1668-1669	TIV-HD1[d] (B1 Victoria) N[c]=420-421	TIV-HD2[e] (B2 Yamagata) N[c]=428	QIV-HD minus TIV-HD (95% CI)	
A (H1N1)[g]	50.4	53.7		-3.27 (-7.37; 0.86)	Yes
A (H3N2)[g]	49.8	50.5		-0.71 (-4.83; 3.42)	Yes
B1 (Victoria)	36.5	39.0	--	-2.41 (-7.66; 2.70)	Yes
B2 (Yamagata)	46.6	--	48.4	-1.75 (-7.04; 3.53)	Yes

[a] NCT03282240
[b] Seroconversion Rates: For subjects with a pre-vaccination titer <10 (1/dil), proportion of subjects with a post-vaccination titer ≥40 (1/dil) and for subjects with a pre-vaccination titer ≥10 (1/dil), proportion of subjects with a ≥four-fold increase from pre-vaccination to post-vaccination titer
[c] N is the number of vaccinated participants with available data for the immunologic endpoint listed
[d] TIV-HD1 contained A/Michigan/45/2015 (H1N1), A/Hong Kong/4801/2014 (H3N2), and B/Brisbane/60/2008 (B1, Victoria lineage)
[e] TIV-HD2 contained A/Michigan/45/2015 (H1N1), A/Hong Kong/4801/2014 (H3N2), and B/Phuket/3073/2013 (B2, Yamagata lineage)
[f] Predefined noninferiority criterion for seroconversion: the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (QIV-HD minus TIV-HD) is >-10%
[g] Pooled TIV-HD group includes subjects vaccinated with either TIV-HD1 or TIV-HD2 for the A strain comparison

Efluelda was as immunogenic as Fluzone High-Dose for GMTs and seroconversion rates for the common influenza strains. Efluelda induced a superior immune response, based on a pre-specified superiority criterion, with respect to the additional B strain than the immune response induced by Fluzone High-Dose formulation that did not contain the additional B strain.

14.2 Efficacy of Fluzone High-Dose in Adults 65 Years of Age and Older

The efficacy of Fluzone High-Dose (trivalent formulation) is relevant to Efluelda since both vaccines are manufactured according to the same process and have overlapping compositions.

Study 2 (NCT01427309) was a multi-center, double-blind, post-licensure efficacy trial conducted in the U.S. and Canada in which adults 65 years of age and older were randomized (1:1) to receive either Fluzone High-Dose or Fluzone. The study was conducted over two influenza seasons (2011-2012 and 2012-2013); 53% of participants enrolled in the first year of the study were re-enrolled and re-randomized in the second year. The per-protocol analysis set for efficacy assessments included 15,892 Fluzone High-Dose recipients and 15,911 Fluzone recipients. The majority (67%) of participants in the per-protocol analysis set for efficacy had one or more high-risk chronic comorbid conditions.

In the per-protocol analysis set, females accounted for 57.2% of participants in the Fluzone High-Dose group and 56.1% of participants in the Fluzone group. In both groups, the median age was 72.2 years (range 65 through 100 years). Overall, most participants in the study were White

(95%); approximately 4% of study participants were Black, and approximately 6% reported Hispanic ethnicity.

The primary endpoint of the study was the occurrence of laboratory-confirmed influenza (as determined by culture or polymerase chain reaction) caused by any influenza viral type/subtype in association with influenza-like illness (ILI), defined as the occurrence of at least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing, or difficulty breathing; concurrent with at least one of the following systemic signs or symptoms: temperature >99.0°F (>37.2°C), chills, tiredness, headaches or myalgia. Participants were monitored for the occurrence of a respiratory illness by both active and passive surveillance, starting 2 weeks post-vaccination for approximately 7 months. After an episode of respiratory illness, nasopharyngeal swab samples were collected for analysis; attack rates and vaccine efficacy were calculated (see Table 5).

Table 5: Study 2[a]: Relative Efficacy Against Laboratory-Confirmed Influenza[b] Regardless of Similarity to the Vaccine Components, Associated with Influenza-Like Illness[c], Adults 65 Years of Age and Older

	Fluzone High-Dose N[d]=15,892 n[e] (%)	Fluzone N[d]=15,911 n[e] (%)	Relative Efficacy % (95% CI)
Any type/subtype[f]	227 (1.43)	300 (1.89)	24.2 (9.7; 36.5)[g]
Influenza A	190 (1.20)	249 (1.56)	23.6 (7.4; 37.1)
A (H1N1)	8 (0.05)	9 (0.06)	11.0 (-159.9; 70.1)
A (H3N2)	171 (1.08)	222 (1.40)	22.9 (5.4; 37.2)
Influenza B[h]	37 (0.23)	51 (0.32)	27.4 (-13.1; 53.8)

[a] NCT01427309
[b] Laboratory-confirmed: culture or polymerase-chain-reaction–confirmed
[c] Occurrence of at least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing, or difficulty breathing; concurrent with at least one of the following systemic signs or symptoms: temperature >99.0°F, chills, tiredness, headaches or myalgia
[d] N is the number of vaccinated participants in the per-protocol analysis set for efficacy assessments
[e] n is the number of participants with protocol-defined influenza-like illness with laboratory confirmation
[f] Primary endpoint
[g] 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.
[h] In the first year of the study the influenza B component of the vaccine and the majority of influenza B cases were of the Victoria lineage; in the second year the influenza B component of the vaccine and the majority of influenza B cases were of the Yamagata lineage

A secondary endpoint of the study was the occurrence of culture-confirmed influenza caused by viral types/subtypes antigenically similar to those contained in the respective annual vaccine formulations in association with a modified CDC-defined ILI, defined as the occurrence of a temperature >99.0°F (>37.2°C) with cough or sore throat. The efficacy of Fluzone High-Dose relative to Fluzone for this endpoint was 51.1% (95% CI: 16.8; 72.0).

14.3 Effectiveness of TIV-HD in Adults 65 Years of Age and Older

Randomised Clinical Trials

A cluster-randomised, controlled clinical trial in United States nursing homes assessed the relative effect of TIV-HD versus a standard dose of influenza vaccine in hospitalisations among 53,008 individuals during the 2013-2014 influenza season.

During the 2013-2014 season, when adjusting for the pre-specified patient and facility characteristics, the incidence of respiratory-related hospital admissions (primary objective) was significantly reduced in facilities where residents received TIV-HD compared with those that received standard-dose influenza vaccines by 12.7% (adjusted risk ratio [ARR] 0.873, 95% CI 0.776 to 0.982, p=0.023). Moreover, with respect to secondary endpoints, TIV-HD reduced hospital admissions for pneumonia by 20.9% (ARR 0.791, 95% CI: 0.267 to 0.953, p=0.013) and all-cause hospital admissions by 8% (ARR 0.915, 95% CI: 0.863 to 0.970, p=0.0028).

Observational Studies

Several retrospective studies, over 10 influenza seasons and in more than 34 million individuals 65 years of age and older, confirmed the superior protection offered by TIV-HD compared to standard-dose influenza vaccines against complications of influenza such as pneumonia hospitalisation (27.3% [95% CI 15.3–37.6%], p<0.001)), cardio-respiratory hospitalisations 17.9% [95% CI 15.0–20.8%], p<0.001) and all–cause hospitalisation 8.4% [95% CI 5.7–11.0%], p<0.001); although the impact may vary per season.

15 REFERENCES

1 Lasky T, Terracciano GJ, Magder L, et al. The Guillain-Barré syndrome and the 1992-1993 and 1993-1994 influenza vaccines. N Engl J Med 1998;339:1797-802.

2 Baxter, R, et al. Lack of Association of Guillain-Barré Syndrome with Vaccinations. Clin Infect Dis 2013;57(2):197-204.

3 Hannoun C, Megas F, Piercy J. Immunogenicity and protective efficacy of influenza vaccination. Virus Res 2004;103:133-138.

4 Hobson D, Curry RL, Beare AS, Ward-Gardner A. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. J Hyg Camb 1972;70:767-777.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Single-dose, prefilled syringe, without needle, 0.7 mL (not made with natural rubber latex). Supplied as package of 1, 5, 10 .

16.2 Storage and Handling

Store Efluelda 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.

17 PATIENT COUNSELING INFORMATION

- Inform the patient or caregiver that Efluelda contains killed viruses and cannot cause influenza.
- Efluelda stimulates the immune system to produce antibodies that help protect against influenza.
- Instruct that annual influenza vaccination is recommended.

Efluelda is a registered trademark of Sanofi Pasteur Inc.

Manufactured by:
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Swiftwater, PA 18370 USA

Importer
Sanofi Pasteur Ltd. – Bangkok, Thailand