אפריל 2024

Efluelda

חומר פעיל:

Influenza virus (inactivated, split) of the following strains*:

A/Victoria/4897/2022 (H1N1) pdm09-like strain (A/Victoria/4897/2022, IVR-238) - 60 micrograms HA**

A/Darwin/9/2021 (H3N2)-like strain (A/Darwin/9/2021, SAN-010) - 60 micrograms HA**

B/Austria/1359417/2021-like strain (B/Michigan/01/2021, wild type) - 60 micrograms HA**

B/Phuket/3073/2013-like strain (B/Phuket/3073/2013, wild type) - 60 micrograms HA**

Per 0.7 ml dose

*propagated in embryonated chicken eggs

**haemagglutinin

חברת סאנופי מבקשת להודיע על כך שאושרה הרחבת ההתוויה לטיפול במבוגרים מגיל 60 שנים ומעלה, כאשר ההתוויה העדכנית הינה:

Efluelda is indicated for active immunisation in adults 60 years of age and older for the prevention of influenza disease.

The use of Efluelda should be based in accordance with official recommendations on vaccination against influenza.

העלון לצרכן במתכונת עלון לרופא ובו מסומנים העדכונים העיקריים מצורף למכתב זה.

העלון המעודכן נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלו מודפס על ידי פנייה לבעל הרישום - סאנופי ישראל בע"מ, Greenwork Park, מתחם העסקים בקיבוץ יקום, בניין E (קומה 1), 6097600, יקום או בטלפון: 09-8633081.

להלן הקישור לאתר משרד הבריאות: https://israeldrugs.health.gov.il/#!/byDrug

בברכה,

חברת סאנופי ישראל בע"מ

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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Efluelda , suspension for injection in pre-filled syringe

Quadrivalent influenza vaccine (split virion, inactivated), 60 micrograms HA/strain

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Influenza virus (inactivated, split) of the following strains*:A/Victoria/4897/2022 (H1N1) pdm09-like strain (A/Victoria/4897/2022, IVR-238) 60 micrograms HA**

A/Darwin/9/2021(H3N2)-like strain (A/Darwin/9/2021, SAN-010) 60 micrograms HA**

B/Austria/1359417/2021-like strain (B/Michigan/01/2021, wild type) 60 micrograms HA**

B/Phuket/3073/2013-like strain (B/Phuket/3073/2013, wild type) .....60 micrograms HA**

Per 0.7 ml dose

* propagated in embryonated chicken eggs

** haemagglutinin

This vaccine complies with the WHO recommendations (Northern Hemisphere) and EU decision for the 2023/2024 season.

Efluelda may contain traces of eggs, such as ovalbumin, formaldehyde which are used during the manufacturing process (see Section 4.3).

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection, in a pre-filled syringe
Efluelda, after shaking gently, is a colourless opalescent liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Efluelda is indicated for active immunisation in adults ~~65~~ 60 years of age and older for the prevention of influenza disease.

The use of Efluelda should be based in accordance with official recommendations on vaccination against influenza.

4.2 Posology and method of administration

Posology

In adults ~~65~~ 60 years of age and older: one dose of 0.7 ml.

Paediatric population
The safety and effectiveness of Efluelda in children less than 18 years of age have not been established.

Method of administration

The preferred route of administration for this vaccine is intramuscular although it may also be given subcutaneously.

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

For instructions on preparation of the medicinal product before administration, see Section 6.6.

4.3 Contraindications

[…]

4.4 Special warnings and precautions for use

[…]

4.5 Interaction with other medicinal products and other forms of interaction

[…]

4.6 Fertility, pregnancy and lactation

Efluelda is only indicated for use in adults aged ~~65~~ 60 years and older.

Efluelda has not been clinically evaluated in pregnant and breast-feeding women.

Pregnancy

[…]

Breastfeeding

[…]

Fertility

[…]

4.7 Effects on ability to drive and use machines

[…]

4.8 Undesirable effects

a. Summary of the safety profile

Adverse event information is based on data coming from ~~one~~two- clinical trial with Efluelda and on the clinical and post-marketing experience of Trivalent Influenza Vaccine (Split Virion, Inactivated) High-Dose (TIV-HD).

The safety of Efluelda was assessed in a pooled analysis of two clinical trials (QHD00013 and QHD00011) in which 2549 adults from 60 years of age and older (378 adults from 60 to 64 years of age and 2171 adults 65 years of age and older) received Efluelda.~~The safety of Efluelda was assessed in one randomized, active-controlled, modified double- blind Phase III clinical trial conducted in the US in which 2670 adults over 65 years of age received one dose (0.7 mL) ofEfluelda or TIV-HD. The safety analysis set included 1777 Efluelda recipients, 443 TIV-HD recipients, and 450 TIV-HD containing the alternate B influenza strain recipients.~~

The most frequently reported adverse reaction occurring after vaccination was injection site pain reported by 42.6~~41.3~~% of study participants followed by myalgia (23.8~~22.7~~%), headache (17.3~~14.4~~%) and malaise (15.6~~13.2~~%). Most of these reactions occurred and resolved within three days of vaccination. The intensity of most of these reactions was mild to moderate.

Overall, adverse reactions were generally less frequent in participants aged 65 years and older than in participants aged 60 to 64 years.

Reactogenicity of the vaccine was slightly increased as compared to the standard dose vaccine, but no major difference in intensity was observed.
The safety of Efluelda was evaluated in a descriptive study (QHD00028) in which subjects received Efluelda together with an investigational booster 100 mcg dose of COVID- 19 mRNA vaccine (nucleoside modified) (n=100), Efluelda only (n=92) or an investigational booster 100 mcg dose of COVID-19 mRNA vaccine (nucleoside modified) only (n=104). The frequency and severity of local and systemic adverse reactions was similar in subjects who were co-administered with Efluelda and licensed COVID-19 mRNA vaccine and subjects administered with a booster dose of licensed COVID-19 mRNA vaccine.

b. Tabulated list of adverse reactions

The data below summarizes the frequencies of adverse reactions that were recorded following vaccination with Efluelda ~~during QHD00013 clinical trial (1777 adults 65 years of age and older)~~ and adverse reactions reported during clinical development and post-marketing experience with TIV-HD (marked with * in the table below).

Adverse events are ranked under headings of frequency using the following convention:

Very common (≥1/10);

Common (≥1/100 to <1/10);

Uncommon (≥1/1,000 to <1/100);

Rare (≥1/10,000 to <1/1,000);

Very rare (<1/10,000);

Not known (cannot be estimated from available data).

ADVERSE REACTIONS	FREQUENCY
General Disorders and Administration Site Conditions	
Injection site pain, injection site erythema, malaise	Very common
~~Injection site erythema, i~~Injection site swelling, injection site induration, injection site bruising, Fever (≥37.5°C), ~~Shivering~~shivering	Common
~~Fever (≥37.5°C), I~~injection site pruritis~~. Asthenia~~, fatigue	Uncommon
~~Fatigue~~Asthenia	Rare
Chest pain	Not known*
Musculoskeletal and Connective Tissue Disorders	
Myalgia	Very common
Muscle weakness[a]~~weakness~~	Uncommon
Arthralgia, pain in extremities	Rare
Nervous System Disorders	
Headache	Very common
Lethargy[a]~~Lethargy~~	Uncommon
Dizziness, paraesthesia	Rare
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)~~, paraesthesia~~	Not known*
Blood and Lymphatic System Disorders	
Thrombocytopenia, lymphadenopathy	Not known*

ADVERSE REACTIONS	FREQUENCY
Respiratory, Thoracic and Mediastinal Disorders	
Cough, oropharyngeal pain	Uncommon
Rhinorrhea	Rare
Dyspnea, wheezing, throat tightness~~, oropharyngeal pain, and rhinorrhea~~	Not known*
Gastrointestinal Disorders	
~~Diarrhoea, nausea, dyspepsia~~Nausea, vomiting, dyspepsia[a], diarrhoea	Uncommon
~~Vomiting~~	~~Rare~~
Immune System Disorders	
~~Night sweats, rash~~	~~Uncommon~~
Pruritus, urticaria, night sweats, rash	Rare
Anaphylaxis, other allergic/hypersensitivity reactions (including angioedema)	Not known*
Vascular Disorders	
Flushing	Rare
Vasculitis, vasodilatation	Not known*
Ear and Labyrinth Disorders	
Vertigo	~~Uncommon~~Rare
Eye Disorders	
Ocular hyperemia	~~Not known*~~Rare

[a]Dyspepsia, lethargy, and muscular weakness were observed with TIV-HD in the QHD00013 trial

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health (www.health.gov.il) according to the National Regulation by using an online form https://sideeffects.health.gov.il.

4.9 Overdose

Cases of administration of more than the recommended dose have been reported with TIV-HD associated with inadvertent use in the population below ~~65~~ 60 years of age due to medication error. When adverse reactions were reported, the information was consistent with the known safety profile of TIV-HD.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccine, ATC code: J07BB02.

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

Pharmacodynamic effects

Immunogenicity - QHD00013

A randomized, active-controlled, modified double-blind Phase III clinical trial was conducted in the US in adults 65 years and older.

The objective was to demonstrate the noninferiority of Efluelda over TIV-HD, as assessed by HAI (hemagglutinin inhibition) Geometric mean antibody titers (GMTs) at Day 28 and seroconversion rates.

A total of 2670 adults from 65 years of age were randomized to receive either one dose of Efluelda or one dose of TIV-HD (one of two formulations of comparator vaccine [TIV-HD1 or TIV-HD2]); each TIV HD formulation contained a B strain that corresponds to one of the two B strains in Efluelda (either a B strain of the Yamagata lineage or a B strain of the Victoria lineage).

The immunogenicity results ~~of Efluelda in the QHD00013 study~~ are summarized below in **Table** 1.

Table 1: Study 1a: Analyses of Noninferiority of Efluelda Relative to TIV-HD by Post-Vaccination HAI Antibody GMTs and Seroconversion Rates in Adults 65 Years of Age and Older, Per-Protocol Analysis Set

Influenza Strain	GMT			GMT Ratio	Seroconversion Rate (Percentage)[b]			Difference of Seroconversion Rates	Met Pre-defined Noninferiority Criteria[f]
	QIV-HD (Efluelda) N[c]=1679-1680 (95% CI)	TIV-HD1[d] (B1 Victoria) N[c]=423 (95% CI)	TIV-HD2[e] (B2 Yamagata) N[c]=430 (95% CI)	QIV-HD over TIV-HD (95% CI)	QIV-HD (Efluelda) N[c]=1668-1669 (95% CI)	TIV-HD1[d] (B1 Victoria) N[c]=420-421 (95% CI)	TIV-HD2[e] (B2 Yamagata) N[c]=428 (95% CI)	QIV-HD (Efluelda) minus TIV-HD (95% CI)	
A (H1N1) [g]	312 (292; 332)	374 (341; 411)		0.83 (0.744; 0.932)	50.4 (48.0; 52.8)	53.7 (50.2; 57.1)		-3.27 (-7.37; 0.86)	Yes
A (H3N2) [g]	563 (525; 603)	594 (540; 653)		0.95 (0.842; 1.066)	49.8 (47.3; 52.2)	50.5 (47.1; 53.9)		-0.71 (-4.83; 3.42)	Yes
B1 (Victoria)	516 (488; 545)	476 (426; 532)	--	1.08 (0.958; 1.224)	36.5 (34.2; 38.9)	39.0 (34.3; 43.8)	--	-2.41 (-7.66; 2.70)	Yes
B2 (Yamagata)	578 (547; 612)	--	580 (519; 649)	1.00 (0.881; 1.129)	46.6 (44.2; 49.0)	--	48.4 (43.5; 53.2)	-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- 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 rates: the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (Efluelda minus TIV-HD) is >-10%. Predefined noninferiority criterion for the GMT ratio: the lower limit of the 95% CI of the GMT ratio (Efluelda divided by TIV-HD) is >0.667.

[g] For the A strain comparison, TIV-HD1 and TIV-HD2 were pooled into a TIV-HD group for comparison with Efluelda.

Efluelda was as immunogenic as TIV-HD for GMTs and seroconversion rates for the common influenza strains. Moreover, Efluelda induced a superior immune response with respect to the additional B strain than the immune response induced by TIV-HD that does not contain the corresponding B.

The efficacy and effectiveness results of TIV-HD are thus inferred to Efluelda given the demonstration of statistically comparable immunogenicity between TIV-HD and Efluelda in the QHD00013 study.

QHD00011

A randomized, active-controlled, modified double-blind, Phase III clinical trial conducted in Europe in adults 60 years and older to demonstrate the superiority of Quadrivalent Influenza Vaccine (Split Virion, Inactivated) HighDose over QIV-SD for all strains, as assessed by HAI (hemagglutinin inhibition) geometric mean antibody titers (GMTs) at Day 28 in adults 60 to 64 years of age and in adults 65 years of age and older.

A total of 1539 adults (760 adults 60 to 64 years of age and 779 adults 65 years of age and older) were randomized to receive either one dose of Quadrivalent Influenza Vaccine (Split Virion, Inactivated) HighDose or one dose of QIV-SD.

Table 2: Study 2a: Analyses of Superiority of Quadrivalent Influenza Vaccine (Split Virion, Inactivated) HighDDose Relative to QIV-SD by Post-Vaccination HAI Antibody GMTs in Adults 60-64 Years of Age and 65 Years of Age and Older, Full Analysis Set

Influenza Strain	Adults 60 to 64 Years of Age			Met Pre-defined Superiority Criteria[c]	Adults 65 years of Age and Older			Met Pre-defined Superiority Criteria[c]
	GMT		GMT Ratio		GMT		GMT Ratio	
	QIV-HD N[b]=376-377 (95% CI)	QIV-SD N[b]=377 (95% CI)	QIV-HD over QIV-SD (95% CI)		QIV-HD N[b]=392 (95% CI)	QIV-SD N[b]=381 (95% CI)	QIV-HD over QIV-SD (95% CI)	
A (H1N1)	471 (416 ; 533)	248 (217 ; 283)	1.90 (1.58 ; 2.28)	Yes	286 (250 ; 326)	162 (139 ; 190)	1.76 (1.44 ; 2.15)	Yes
A (H3N2)	303 (262 ; 350)	178 (154 ; 206)	1.70 (1.38 ; 2.08)	Yes	324 (281 ; 374)	151 (129 ; 176)	2.15 (1.74 ; 2.65)	Yes
B1 (Victoria)	497 (450 ; 548)	330 (297 ; 367)	1.51 (1.30 ; 1.74)	Yes	405 (366 ; 447)	262 (236 ; 291)	1.55 (1.34 ; 1.79)	Yes
B2 (Yamagata)	766 (690 ; 849)	433 (391 ; 480)	1.77 (1.53 ; 2.04)	Yes	536 (485 ; 592)	305 (274 ; 340)	1.76 (1.52 ; 2.03)	Yes

[a] NCT04024228
[b] N is the number of participants with available data for the considered endpoint
[c] Superiority was concluded if the lower limit of the two-sided 95% CI of the ratio of GMTs between groups (QIV-HD/QIV-SD) was > 1 for each strain and in each age group

The efficacy and effectiveness results of TIV-HD are thus inferred to Quadrivalent Influenza Vaccine (Split Virion, Inactivated) HighDose, given the demonstration of statistically comparable immunogenicity between TIV-HD and Quadrivalent Influenza Vaccine (Split Virion, Inactivated) HighDose in adults 65 years of age and older (QHD00013) and similar immune responses observed in adults 60 to 64 years of age and in adults 65 years of age and older (QHD00011).

In addition, Quadrivalent Influenza Vaccine (Split Virion, Inactivated) HighDose induced an immune response that was superior to the responses induced by QIV-SD for all 4 virus strains 28 days post-vaccination in adults 60 to 64 years of age and in adults 65 years of age and older.

Pivotal Clinical Efficacy (FIM12)

FIM12 was a multi-centre, double-blind efficacy trial conducted in the US and Canada in which adults 65 years of age and older were randomised (1:1) to receive the TIV-HD or a standard dose vaccine. The study was conducted over two influenza seasons (2011-2012 and 2012-2013) to assess the occurrence of laboratory-confirmed influenza caused by any influenza viral type/subtype, in association with influenza-like illness (ILI) as the primary endpoint.

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. The pre-specified statistical superiority criterion for the primary endpoint (lower limit of the 2-sided 95% CI of the vaccine efficacy for the TIV-HD relative to standard dose vaccine > 9.1%) was met.

Table ~~2~~3: Relative vaccine efficacy to prevent influenza-like illness[a] in adults ≥ 65 years

	High Dose vaccine N[b]=15892 n[c] (%)	**Standard dose vaccine N[b]=15911 n[c] (%)**	**Relative Efficacy % (95% CI)**
Laboratory-confirmed influenza[d] caused by:			
- **Any type/subtype[e]**	227 (1.43)	300 (1.89)	24.2 (9.7; 36.5)
- **Viral strains similar to those contained in the vaccine**	73 (0.46)	113 (0.71)	35.3 (12.4; 52.5)

[a]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 >37.2°C, chills, tiredness, headaches or myalgia

[b]N is the number of vaccinated participants in the per-protocol analysis set for efficacy assessments

[c]n is the number of participants with protocol-defined influenza-like illness with laboratory confirmation

[d]Laboratory-confirmed: culture- or polymerase-chain-reaction-confirmed

[e]Primary endpoint

Effectiveness Studies

[…]

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

[…]

6 PHARMACEUTICAL PARTICULARS

[…]

7 MARKETING AUTHORISATION HOLDER

Sanofi Israel Ltd., Greenwork Park, P.O box 47, Yakum

8 MARKETING AUTHORISATION NUMBER(S)

169-15-36617

Revised in March~~December~~ ~~2023~~ 2024 according to MoH guidelines.