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 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 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

Hypersensitivity to the active substances or to any of the excipients listed in Section 6.1 or to any component that may be present as traces such as eggs (ovalbumin, chicken proteins) and formaldehyde.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name of the administered product should be clearly recorded. It is recommended to record the batch number as well.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Efluelda should under no circumstances be administered intravascularly.

Vaccination should be postponed in patients with acute febrile illness until the fever is resolved.

If Guillain-Barré syndrome (GBS) has occurred within 6 weeks of any previous influenza vaccination, the decision to give Efluelda should be based on careful consideration of the potential benefits and risks.

As with other vaccines administered intramuscularly, the vaccine should be administered with caution to subjects with thrombocytopaenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent injury from fainting and manage syncopal reactions.

Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.

As with any vaccine, a protective response may not be elicited in all vaccine recipients.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium free".

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of Quadrivalent Influenza Vaccine (Split Virion, Inactivated) High Dose with an investigational booster 100 mcg dose of COVID-19 mRNA vaccine (nucleoside modified/elastomeran) has been evaluated in a limited number of participants in a descriptive clinical study (see sections 4. And 5.1). If Efluelda needs to be given at the same time as another injectable vaccine(s), immunisation should be carried out on separate limbs.

It should be noted that the adverse reactions may be intensified by any co-administration.

The immunological response may be reduced if the patient is undergoing immunosuppressant treatment.

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 reported. 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 influenza vaccine.

4.6 Fertility, pregnancy and lactation

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

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

Pregnancy

Inactivated influenza standard dose vaccines (15 micrograms haemagglutinin of each virus strain per dose) can be used in all stages of pregnancy. Larger datasets on safety are available for the second and third trimester, compared with the first trimester. Data from worldwide use of inactivated influenza standard dose vaccines do not indicate any adverse foetal and maternal outcomes attributable to the vaccine. However, data on the use of influenza vaccines containing 60 micrograms haemagglutinin of each virus strain per dose in pregnant women are limited.

Breastfeeding

Efluelda may be used during breast-feeding. Based on experience with standard dose vaccines, no effects on the breast-fed infant are anticipated.

Fertility

Efluelda has not been evaluated for possible effects on human fertility.

4.7 Effects on ability to drive and use machines

Efluelda has no or negligible influence on the 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 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 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 41.3% of study participants followed by myalgia (22.7%), headache (14.4%) and malaise (13.2%). Most of these reactions occurred and resolved within three days of vaccination.

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, malaise	Very common
Injection site erythema, injection site swelling, injection site induration, injection site bruising, Shivering	Common
Fever (≥37.5°C), injection site pruritis. asthenia	Uncommon
Fatigue	Rare
Chest pain	Not known*
Musculoskeletal and Connective Tissue Disorders	
Myalgia	Very common
Muscle weakness	Uncommon
Arthralgia, pain in extremities	Rare
Nervous System Disorders	
Headache	Very common
Lethargy	Uncommon
Dizziness	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	Uncommon
Dyspnea, wheezing, throat tightness, oropharyngeal pain, and rhinorrhea	Not known*
Gastrointestinal Disorders	
Diarrhoea, nausea, dyspepsia	Uncommon
Vomiting	Rare
Immune System Disorders	
Night sweats, rash	Uncommon
Pruritus, urticaria	Rare
Anaphylaxis, other allergic/hypersensitivity reactions (including angioedema)	Not known*
Vascular Disorders	
Flushing	Rare
Vasculitis, vasodilatation	Not known*
Ear and Labyrinth Disorders	
Vertigo	Uncommon
Eye Disorders	
Ocular hyperemia	Not known*

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 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.

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: 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

Randomized Clinical Trials

A cluster-randomized, controlled clinical trial in United States nursing homes assessed the relative effect of TIV-HD versus a standard dose of influenza vaccine in hospitalizations among 53008 individuals during the 2013-2014 influenza season.

During the 2013-2014 season, 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 8 influenza seasons and in more than 24 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 and influenza hospitalization (13.4% (95%CI: 7.3% to 19.2%, p<0.001)), cardio-respiratory hospitalizations 17.9% (95%CI :14.9% to 20.9%, p<0.001) and all –cause hospitalization 8.1% (95%CI: 5.9% to 10.3%, p<0.001) ; although the impact may vary per season.

Concomitant Administration with COVID-19 mRNA Vaccine (nucleoside modified)

In a descriptive open-label clinical study (NCT04969276), healthy adults aged 65 years and older were divided in three groups: Group 1 received Efluelda alone (N=92), Group 2 (N=100) received Efluelda concomitantly with an investigational booster 100 mcg dose of COVID-19 mRNA vaccine (nucleoside modified) at least 5 months after the second dose of the primary series, Group 3 (N=104) received only the investigational booster 100 mcg dose of COVID-19 mRNA vaccine (nucleoside modified).

Co-administration resulted in no change to influenza vaccine immune responses as measured by hemagglutination inhibition (HAI) assay. Co-administration resulted in similar responses to COVID-19 mRNA vaccine, as assessed by an anti-spike IgG assay (see section 4.5 and 4.8).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Nonclinical data reveal no special hazards for humans based on conventional studies of local tolerance and repeated dose toxicity studies.

Efluelda has not been evaluated for carcinogenic or mutagenic potential nor for developmental and reproductive toxicity study.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Sodium phosphate-buffered isotonic sodium chloride solution
    - Sodium chloride
    - Monobasic sodium phosphate
    - Dibasic sodium phosphate
    - Water for injections
- Octoxinol-9

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze. Keep the syringe in the outer carton in order to protect from light.

6.5 Nature and contents of container

0.7 ml of suspension in pre-filled syringe (Type I glass) without needle, equipped with a plunger stopper (bromobutyl rubber) and a tip-cap – pack size of 1, 5 or 10.

0.7 ml of suspension in pre-filled syringe (Type I glass) with separate needle, equipped with a plunger stopper (bromobutyl rubber) and a tip-cap – pack size of 1, 5 or 10.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The vaccine should be allowed to reach room temperature before use.

Shake before use.

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

The syringe is intended for single use only and should not be reused. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER(S)

169-15-36617

Revised in December 2023 according to MoH guidelines.