Date: 31 March 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Efluelda

International non-proprietary name: haemagglutininum influenzae A (H1N1), haemagglutininum influenzae A (H3N2), haemagglutininum influenzae B (Victoria), haemagglutininum influenzae B (Yamagata)

Pharmaceutical form: Suspension for injection in pre-filled syringe

Dosage strength: 1 dose (0.7 mL) contains 60 micrograms split influenza virus of each of the 4 inactivated strains:

Route(s) of administration: i.m., s.c.

Marketing Authorisation Holder: Sanofi-Aventis (Suisse) SA

Marketing Authorisation No.: 67704

Decision and Decision date: approved on 21 July 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of the SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AR	Adverse reaction
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
CBER	Center for Biologics Evaluation and Research
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ELLA	Enzyme-linked lectin assay
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
GMT	Geometric mean titre
HA	Haemagglutinin
HAI	Hemagglutination inhibition
HI	Haemagglutination inhibition
ICH	International Council for Harmonisation
Ig	Immunoglobulin
ILI	Influenza-like illness
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NA	Neuraminidase
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
QIV-HD	High-dose quadrivalent influenza vaccine
RMP	Risk Management Plan
SAE	Serious adverse event
SN	Seroneutralisation
SwissPAR	Swiss Public Assessment Report
TIV-HD	High-dose trivalent influenza vaccine
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substances haemagglutininum influenzae A (H1N1), haemagglutininum influenzae A (H3N2), haemagglutininum influenzae B (Victoria) haemagglutininum influenzae B (Yamagata)

2.2 Indication and Dosage

2.2.1 Requested Indication

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

2.2.2 Approved Indication

Efluelda is used for active immunisation of adults aged 65 years and older for prophylaxis of influenza caused by the two influenza A virus subtypes and the two influenza B virus subtypes contained in the vaccine.
Efluelda must be used in accordance with the official vaccination recommendations.

2.2.3 Requested Dosage

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

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	24 March 2020
Formal control completed	14 May 2020
Predecision	19 June 2020
Answers to Predecision	14 August 2020
Labelling corrections	13 November 2020
Answers to Labelling corrections	14 December 2020
Labelling corrections	22 March 2021
Answers to Labelling corrections	22 April 2021
Final Decision	21 July 2021
Decision	approval

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3 Medical Context

Influenza is a respiratory illness caused by influenza viruses that infect the nose, throat, and lungs. Some people, such as older people, young children, and people with certain health conditions, are at higher risk of serious flu complications. There are two main types of influenza (flu) viruses: Types A and B. The influenza A and B viruses that routinely spread in people (human influenza viruses) are responsible for seasonal flu epidemics each year.
Seasonal influenza causes 4 -50 million symptomatic cases in EU/EEA each year, and 15,000 – 70,000 European citizens die every year of causes associated with influenza. Despite the often short duration of the illness, the yearly economic and healthcare burden of influenza is substantial.
In Switzerland each year influenza leads to 112,000 to 275,000 medical consultations (according to the Sentinella monitoring system). Due to its complications, flu is responsible for thousands of hospitalisations and a few hundred fatalities each year. People with an increased risk of flu complications (pregnant women, infants, elderly people and people with certain chronic diseases) are particularly prone to such outcomes.
(https://www.bag.admin.ch/bag/en/home/krankheiten/krankheiten-im-ueberblick/grippe.html)
Vaccination against influenza is the cornerstone public health intervention to reduce the annual burden of influenza epidemics. The most widely used influenza vaccines are inactivated influenza vaccines, administered intramuscularly.
In the elderly population, changes in B cell and T cell development and function due to the ageing of the immune system, called immunosenescence, result in a decline in the antibody and cellular response to influenza vaccination.
The haemagglutination inhibition (HI) assay is the standard measure of strain-specific antibody titres, and the rise in HI antibody titres with vaccination is usually used to estimate vaccine efficacy in clinical trials.
In some human challenge studies, HI antibody titres of ≥ 1:40 are associated with protection from influenza illness in up to 50% of subjects.
The seasonal influenza vaccine composition for the Northern hemisphere is recommended by the WHO in the first quarter of every calendar year based on the circulating viruses.

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4 Quality Aspects

4.1 Drug Substance

The active substance consists of four monovalent suspension bulks of purified virus antigen of influenza strains, haemagglutinin (HA) and neuraminidase (NA), from each of the specific four influenza virus strains that are recommended for the seasonal formulation every year by the WHO and CHMP. The four strains used in the quadrivalent influenza vaccine consist of one influenza A (H1N1) virus strain, one influenza A (H3N2) virus strain, one influenza B (Yamagata lineage) virus strain, and one influenza B (Victoria lineage) virus strain. The HA and NA proteins used to produce the vaccine are intended to elicit a serological immune response to each of the virus strains included in the vaccine. Each active substance (monovalent bulk) is prepared by propagation of the specific influenza virus strain in fertilised/embryonated hen's eggs. The eggs are harvested, and the allantoic fluid containing the viruses is processed by several purification steps (centrifugation, sucrose gradient, (dia-)filtration) including virus inactivation and solubilisation steps. The manufacturing process has been validated with full-scale drug substance batches. All the analytical methods are described and non-compendial methods have been validated in accordance with ICH guidelines The drug substance is stored at 1-5°C. No significant changes are observed within the proposed storage conditions. A shelf life of 12 months has been accepted.

4.2 Drug Product

The finished product is presented as a colourless opalescent suspension supplied in a pre-filled syringe ready for use. One human dose consists of 0.7 mL suspension. The formulation is prepared to contain the minimum dose of 60 µg haemagglutinin antigen from each of the four virus strains. The antigens are diluted in a clear, sterile, buffered aqueous solution containing sodium chloride (isotonic), disodium hydrogen phosphate (buffer), sodium dihydrogen phosphate (buffer) and octoxynol-9 (stabiliser). The finished product manufacturing process includes e.g. blending of monobulk lots of four strains and dilution with buffer to produce the quadrivalent bulk vaccine, sterile filtration, and filling. Process validation studies were conducted at commercial scale. The drug product is stored at 2-8°C. No significant changes are observed within the proposed storage conditions. A shelf life of 12 months has been accepted. The product should not be frozen and should be kept in the outer carton in order to protect it from light.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

Regarding the marketing authorisation application for Efluelda, a high-dose (HD) quadrivalent influenza vaccine (QIV) containing antigens of A/H1N1-like, A/H3N2-like, and B-like strains (B/Yamagata and B/Victoria lineages), Swissmedic conducted an abridged assessment. The evaluation was based on the approval of FDA in November 2019 and the approval in the decentralised EU process with the related assessment reports provided by the applicant.
Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Efluelda in the proposed indication. There were no safety issues identified in the nonclinical studies that would be of concern for human use. All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

Efluelda is a split virion, inactivated, high-dose quadrivalent influenza vaccine prepared from influenza viruses propagated in embryonated chicken eggs. One dose contains 60 µg of influenza haemagglutinin (HA) from each of the following influenza types or lineages: A/H1N1, A/H3N2, B Victoria, B Yamagata per 0.7 ml dose, complying with the WHO recommendation and EU decision for the respective season.
The clinical development programme for Efluelda was based on the trivalent inactivated high-dose influenza vaccine (TIV-HD) that has not yet been approved in Switzerland or Europe, with the exception of the UK (in 2019). The trivalent vaccine is, however, approved and used in the USA, Australia, Canada and Brazil.
The main information in support of this application comes from two clinical studies with the high-dose quadrivalent influenza vaccine (QIV-HD) (QHD00008, QHD00013) and five clinical studies with the TIV-HD (FIM01, FIM05, FIM07, FIM12 and a Phase IV study GRC75-EXT). Additionally, publications on dose-finding and effectiveness studies with the TIV-HD as published literature were submitted. QHD00013 and FIM12 were considered as pivotal studies.
No pharmacokinetic studies have been conducted for Efluelda, as the examination of pharmacokinetic parameters of vaccines is not generally recommended. This is accepted and in line with the EMA Guideline (EMA/CHMP/VWP/164653/2005).

A vaccine`s pharmacodynamic profile is defined by its immunogenicity.
The pharmacodynamic action of a vaccine is based on inducing preferably neutralising antibodies against the foreseen target/microbe. HA is the major antigen against which the host's protective antibody response is directed and is responsible for the attachment of influenza viruses to oligosaccharide-containing terminal sialic acids on the cell surface during the early stages of infection. In case of influenza vaccines, antibodies against the surface protein haemagglutinin are the most relevant target of the vaccines. A correlation was found between haemagglutination inhibition titre and protection, a 1:40 HI titre is thought to provide 50% protection from influenza infection.

6.2 Dose Finding and Dose Recommendation

The 60 µg HA from each of the influenza subtypes/lineages was selected through dose-finding studies conducted with the TIV-HD. NIH Study DMID Protocol 01-597 was submitted as a publication (Keitel 2006), and a full CSR was available for Study FIM01 (NIH Study 04-100). Immunogenicity data did not demonstrate in all strains substantially higher rates of seroprotection that would correlate with clinical efficacy. Superior efficacy based on seroprotection was suggested for one of the three strains, A/H1N1, in Study FIM01. There were slightly higher geometric mean titres (GMTs), especially with the criterion of "percentage of participants with 4-fold or greater increases in serum antibody titres after immunisation". Higher systemic and local reactogenicity was observed following vaccination with the high-dose vaccine compared to the standard-dose influenza vaccine.

6.3 Efficacy

Two main pivotal studies were submitted to support the application.
QHD00013 (NCT03282240) assessed the safety and immunogenicity of Efluelda compared to the high-dose trivalent influenza vaccine (TIV-HD).
Study **FIM12** was the pivotal efficacy study performed with the TIV-HD and assessed the efficacy against PCR proven Influenza like Illness (ILI) of the TIV-HD (Fluzone High-Dose) compared to a standard-dose trivalent vaccine (Fluzone).
As requested by Swissmedic, Study QHD00011 was additionally submitted with the response to the Preliminary Decision. The request was mainly driven by the need to further expand the safety database for QIV-HD.

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Study QHD00013

QHD00013 was a randomised, modified double-blind, active-controlled, multi-centre study conducted in 2,670 healthy subjects aged 65 years and older.
The study was conducted from September 2017 to April 2018 at 35 centres in the US.
The comparator high-dose trivalent influenza vaccine (TIV-HDs) contained either the B strain from the primary lineage (TIV-HD1, which was the licensed vaccine [Fluzone® High- Dose] for the 2017-2018 Northern Hemisphere influenza season) or the B strain from the alternate lineage (TIV-HD2, which was an investigational TIV-HD containing an alternate B strain).
Subjects were randomised into 3 groups in a 4:1:1 ratio: QIV-HD, TIV-HD1, and TIV-HD2.
Subjects were also randomly assigned to the Expanded Immunogenicity Subset for seroneutralisation (SN) testing and enzyme-linked lectin assay (ELLA) via interactive response technology (IRT). A subset of approximately 100 subjects per treatment groups was identified just after the completion of the enrolment.
Due to the different filling volumes of the vaccines (0.7 ml for QIV-HD and 0.5 ml for the TIV-HD) an unblinded administrator at each site who was not involved in any of the blinded assessments administered the vaccine. The subjects did not know which product was administered.
The inclusion and eligibility criteria used are considered appropriate.
Subject demographics were balanced between the groups, with the exception of gender, as there were more females (57.9% vs 42.1% males in the PPAS). Most of the subjects (74.3%), as expected, had received influenza vaccination in the previous season, and the rates of subjects among the groups were similar. Pre-vaccination hemagglutination inhibition (HAI) GMTs and seroprotection rates were similar between the groups for all strains.
Out of the 2,670 randomised subjects, 16 (0.6%) subjects did not complete the study: 10 (0.6%), 3 (0.7%), and 3 (0.7%) subjects in the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively.
Two subjects each in the QIV-HD and TIV-HD1 groups withdrew due to an AE.
Other reasons for discontinuation were lost to follow-up (3 subjects in the QIV-HD group), protocol deviation (4, 1 and 2 subjects in the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively), and voluntary withdrawal by subject not due to an adverse event (AE) (1 subject each in the QIV-HD and TIV-HD2 groups).
The *primary objective* was to demonstrate that Efluelda induces an immune response (as assessed by HAI geometric mean titres [GMTs] and seroconversion rates) that is non-inferior to responses induced by TIV-HD1 and TIV-HD2 for the 4 virus strains at 28 days post-vaccination in all subjects.
Secondary objectives were:

- To demonstrate that each B strain in the QIV-HD induces an immune response (as assessed by HAI GMTs and seroconversion rates) that is superior to the response induced by the TIV-HD that does not contain the corresponding B strain in all subjects.
- To describe the immune response induced by QIV-HD, TIV-HD1, and TIV-HD2 by the HAI measurement method in all subjects.
- To describe the immune response 28 days after vaccination by the virus SN measurement method in a randomised subset of subjects from each study group.
- To describe the safety profiles of all subjects in each trial group.

For the A strains, the primary objective was evaluated using pooled data from TIV-HD1 and TIV-HD2 groups. For each of the B strains, the primary objective was evaluated based on the TIV-HD group containing the corresponding B strain.
The primary objective of non-inferiority of QIV-HD to TIV-HD as assessed by GMTs and seroconversion rates was met, as the lower limit of the 95% CI was *above 0.667* for the *ratio of GMTs* and *above -10%* for the *differences of seroconversion rates* for all influenza strains.
The predefined non-inferiority margins were acceptable.
For a tabulated presentation of the primary endpoint results please see the "*Efficacy*" section of the information for healthcare professionals.

The *secondary immunogenicity objective*, to demonstrate that each B strain in QIV-HD induces superior immune response (as assessed by HAI GMTs and seroconversion rates) to the response induced by the TIV-HD that does not contain the corresponding B strain, was met, as the lower limit of

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the 95% CI was above 1.5 for the ratios of GMTs and above 10% for the seroconversion rates for both B influenza strains.
For the QIV-HD, TIV-HD1, and TIV-HD2 groups, the percentages of subjects who achieved seroprotection were 95.1%, 96.7%, and 95.6% against the A/H1N1 strain, respectively; 96.9%, 96.9%, and 96.7% against the A/H3N2 strain, respectively; 99.0%, 99.1%, and 96.5% against the B/Brisbane strain, respectively; and 99.3%, 96.7%, and 99.1% against the B/Phuket strain, respectively.
Of note, seroprotection rates for those B strains that are not included in the respective TIV-HD1 or TIV-HD2 were similar to the seroprotection rates for the B strain that is included in the vaccine. This might be the result of cross-reactive antibodies.

Immunogenicity assessed by covariate factors showed lower post-vaccination GMTs and seroconversion rates for subjects over 75 years of age compared to subjects 65-75 years of age. Further subgroup analysis showed higher post vaccination GMTs and seroconversion rates in female than in male subjects and in subjects with no history of previous influenza vaccination the prior year compared to subjects with a history of an influenza vaccination the prior year.

GMTs (pre- and post-vaccination), geometric mean titre ratios (GMTRs), and fold rises (2- and 4-fold) were similar among all study groups for both influenza A strains and for each of the B strains when QIV-HD is compared with the corresponding TIV-HD containing the same B strain when measured by the SN assay.
The anti-NA Ab response against the N1 antigen in the A/H1N1 strain and N2 antigen in the A/H3N2 strain was assessed by ELLA as an additional immunogenicity analysis. The clinical relevance of the immune response measured by the neutralisation and ELLA assays is currently not fully understood; furthermore, there is no correlate of protection established either for the neutralising antibody titres, or for the antibody response against the neuraminidase.

In summary, Efluelda in subjects over 65 years of age demonstrated non-inferior immunogenicity compared to TIV-HD.

Study FIM12
FIM12 was a phase III/IV, randomised, modified double-blind multicentre efficacy study conducted in the USA and Canada with the licensed TIV-HD in healthy adults ≥65 years without moderate-to-severe acute illness.
The efficacy was assessed over two seasons, the first season enrolled 14,500 subjects (7,254 TIV-HD, 7,246 TIV); the second season enrolled 17,489 subjects (8,737 TIV-HD, 8,752 TIV).
There was one primary endpoint with a statistical hypothesis: “Occurrences of culture- or PCR-confirmed influenza (≥ 14 days post-vaccination) caused by any influenza viral type/subtype, in association with a protocol-defined ILI.”
The per protocol ILI definition included low-grade fever >37.2°C in combination of 2 of multiple symptoms (e.g. wheezing and headache without cough and without sore throat). This was not fully in line with the CDC (>37.2°C and cough or sore throat) or with the WHO 2014 ILI definition of fever >38.0°C[1]. For the primary endpoint, Fluzone High-Dose would be considered superior to Fluzone if the lower bound of the CI for relative VE was > 9.1%; 95% of enrolled subjects were evaluable for relative VE.
The primary endpoint with the per protocol ILI definition was fulfilled with 24.24% (95% CI 9.69; 36.52) combined over 2 years. Of note, the lower boundary of the 95% CI was not >9.1% for year 1 and 2 separately, and the additional primary analyses with modified CDC-defined influenza-like illness criteria and with ILI definition associated with respiratory illness were both not statistically significant.
As there were no statistical hypotheses or corrections for multiple testing regarding any of the secondary or observational endpoints or the exploratory endpoints, including effectiveness data on

[1] https://www.who.int/influenza/surveillance_monitoring/ili_sari_surveillance_case_definition/en/

hospitalisations and pneumonia, these are not presented in the information for healthcare professionals.

FIM12 was the successor study of Study FIM07, which was a randomised, double-blind, active-controlled, multi-centre trial assessing the relative efficacy of TIV-HD to that of TIV-SD in adults 65 years of age and older, with respect to laboratory-confirmed influenza illness caused by viral types/subtypes antigenically similar to those contained in the respective annual vaccine formulations. As the primary endpoint regarding matching influenza strains could not be reached due to the A/H1N1 swine flu pandemic in 2009, the study was terminated earlier than planned, after one season.

Study QHD00011
Study QHD00011 compared the immunogenicity and safety of Efluelda to a standard-dose quadrivalent influenza vaccine approved in Switzerland. This was a phase III, randomised, modified double-blind, multicentre study conducted in Europe with approximately 1,540 healthy adults (770 adults 60 to 64 years of age and 770 adults 65 years of age and older).
The primary objective of superiority of QIV-HD to QIV-SD as assessed by HAI GMTs was met, as the lower limit of the two-sided 95% CI was above 1 for the ratio of GMTs for all influenza strains in each age group. A stringent superiority criterion, as defined by a lower bound of the 95% CI for the ratio of geometric mean HAI titres of >1.5, would have been preferable.
The immunogenicity results for subjects over 65 years of age are presented in a tabulated form in the information for healthcare professionals.

Seroconversion and seroprotection rates in both vaccine groups met the CBER criteria (lower bound of the two-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibodies should meet or exceed 30%, and the lower bound of the two-sided 95% CI for the percentage of subjects achieving an HI antibody titre ≥ 1:40 should meet or exceed 60%) for all strains in subjects older than 65 years of age. The rates of seroconversion and seroprotection were, in most cases, numerically higher for the QIV-HD group. See also Table 2 in the information for healthcare professionals for the details.
The immunogenicity/safety and the efficacy of the TIV-HD compared to standard-dose influenza vaccine is relevant, as the higher HA content included in the vaccine needs to be justified with the demonstration of added benefit for the vaccinated population, especially taking into account the higher rate of reactogenicity due to the increased HA amount and the consequently higher amount of impurities
Supportive Study conducted with TIV-HD- FIM05
Study FIM05, after having demonstrated the consistency of three different lots of TIV-HD, assessed as the second primary objective the immunogenicity of the TIV-HD (Fluzone-HD) - pooled data from the three lots - compared to standard-dose TIV (Fluzone). The criterion of superiority was met for both seroconversion and GMT ratios as, according to the protocol, it was sufficient to show superiority for **two** of the three vaccine strains and non-inferiority for the third strain.
Superiority could not be demonstrated for the TIV-HD vaccine over the standard-dose trivalent vaccine for the B strain, based on any of the predefined criteria (seroconversion, GMT ratios). For the B strain non-inferiority criteria were met.

6.4 Safety

The safety database for QIV-HD, consisting of 1,777 +120 subjects from Study QHD00013 and QHD0008, was initially considered to be limited.
Generally, the approval of a new influenza vaccine would require a safety database consisting of approximately 3,000 subjects to fulfil the requirements of the EMA guideline CHMP/VWP/164653/2005 and EMA influenza guideline CHMP/VWP/457259/2014.
Considerable experience has been acquired with the TIV-HD vaccine, with a total of 25,564 subjects exposed to TIV-HD in clinical trials and approximately 104.5 million doses distributed (USA, Canada, and Australia) since 2009. However, there were concerns regarding the extent to which the safety

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data for the TIV-HD from clinical studies could be applied to the QIV-HD, as the manufacturing process had been changed since most of the TIV-HD studies were conducted, and the addition of the second B strain not only increased the HA content, but substantially augmented the total protein content, including impurities. Furthermore, the filling volume was also higher for QIV-HD compared to TIV-HD. For the listed reasons, with the exception of the post-marketing data of TIV-HD, the safety profile needed to be characterised based on QIV-HD specific data.
The additionally requested Study QHD00011 submitted to Swissmedic with the answer to the Preliminary Decision compared the QIV-HD to a standard-dose QIV and provided relevant further information on the safety profile of the vaccine.

Study QHD00013
All subjects were observed for 30 minutes after vaccination, and any unsolicited systemic AEs occurring during that time were recorded as immediate unsolicited systemic AEs. Solicited reactions were collected for 7 days after vaccination, and unsolicited adverse events (AEs) were collected up to Day 28. Serious adverse events (SAEs) and adverse events of special interest (AESIs) were collected up to Day 180 following vaccination.
Safety results were analysed descriptively for subjects in the safety analysis set (SafAS) who received QIV-HD, TIV-HD1, and TIV-HD2. Solicited reactions (solicited injection site and systemic reactions), unsolicited AEs, SAEs, and AESIs were summarised.
Very few subjects were discontinued from the study.
Within 7 days after vaccination, the percentages of subjects who reported at least 1 solicited injection site reaction were **44.1**% (779/1,768) and **39.8%** (354/889) in the QIV-HD and TIV-HD pooled groups, respectively. The most frequently reported solicited injection site reaction was pain, reported by 41.3% in the QIV-HD and 36.4% and TIV-HD pooled groups.

Although the percentage of subjects who reported at least one solicited reaction within 7 days after vaccination were similar between groups, Grade 2 and Grade 3 reactions were reported more often in the QIV-HD group.
The few Grade 3 solicited injection site reactions were reported by 26 (1.5%) and 4 (0.4%) subjects in the QIV-HD and TIV-HD pooled groups, and the reactions were pain 12 (0.7%) vs 2 (0.2%), erythema 11 (0.6%) vs 2 (0.2%), swelling 5 (0.3%) vs 1 (0.1%) and induration 3 (0.2%) vs 1 (0.1%).
This slightly greater reactogenicity is most likely due to the higher HA (and other non-HA protein) content in the QIV-HD vs TIV-HD.

The most frequently reported solicited systemic reaction was myalgia, reported by 22.7% and 18.9% of subjects in the QIV-HD and TIV-HD pooled groups, respectively.

The percentages of SAEs and deaths in the study groups were similar. A total of 128 subjects experienced 162 SAEs during the study.
One subject in the QIV-HD group developed small fibre inflammatory neuropathy 40 days after the vaccination. This was considered by the investigator to be related to the study vaccination, but was considered by the sponsor to be not related to the study vaccination since the event occurred more than 1 month after vaccination (outside of the usual time window for the vast majority of vaccine-related events) and in view of the other aetiologies reported (i.e., vitamin B12 deficiency and recent viral illness), which are more likely causes of the SAE.
However, a causal relation to the vaccination cannot be ruled out.

A total of 5 deaths were reported during the study. Two within 28 days: one in the QIV-HD group, 6 days after vaccination, reported as due to natural causes, although the subject was suspected to have MI, arrhythmia, or massive stroke; the second in the TIV-HD1 group 25 days after vaccination and associated with myocardial infarction. This was a 75-year-old female with a history of CAD, hypercholesterinaemia, COPD, depression, and hypertension.
During the 6-month follow-up period: QIV-HD: 168 days after vaccination: acute respiratory infection in a 75-year-old female patient with a history of COPD. She had been hospitalised due to acute

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exacerbation and died 5 days later. QIV-HD: 105 days after vaccination: prostate cancer with metastasis, blood culture was positive for MSSA, died 6 days later. TIV-HD-1: 87 days after vaccination: pneumonia, 92-year-old male patient with a history of CAD, hypothyroidism, dementia, sleep apnoea, hypertension, peripheral oedema, oesophageal varices, oesophagitis and atrial fibrillation. On day 34 he was admitted to hospital for a syncopal episode and cough. He was diagnosed with pneumonia and was discharged 2 days later on antibiotics. On day 87 pneumonia and sepsis were diagnosed in the hospital and he died 19 days later.
All deaths and AESIs were evaluated as unrelated to the study vaccination. Reported AESIs were few and distributed across the groups, although all (3) involved Bell's palsy. Bell's palsy is included in the draft information for professional healthcare as a post-marketing AE of the trivalent vaccine.
In summary, in Study QHD00013 no new safety concerns were identified in QIV-HD versus TIV-HD, although a slightly greater reactogenicity was observed for the QIV-HD compared to the TIV-HD, which could be explained by the higher amount of HA and impurities.

Study QHD00011
Collection of safety data:
• All subjects were observed for 30 minutes after vaccination. Any unsolicited systemic adverse events (AEs) occurring during that time were recorded as immediate unsolicited systemic AEs in the Case Report Book (CRB).
• Solicited reactions were collected up to 7 days after vaccination (D0 to D7), and unsolicited AEs were collected up to 28 days after vaccination (D0 to D28 [V02]). Subjects were to record this information in a diary card (DC).
• Serious adverse events (SAEs) and adverse events of special interest (AESIs) were, and continue to be, collected throughout the study (D0 up to approximately D180 [6-month follow-up period]). Subjects were asked to notify the site immediately of any potential SAEs (including AESIs) at any time during the study.
• Staff reviewed the V01 (D0) to V02 (D28) safety data with subjects at V02.
• Subjects will continue to collect information on SAEs and AESIs in a memory aid (D28 [V02]-D180). AESIs will be captured as SAEs. These AESIs include new onset of Guillain-Barré syndrome (GBS), encephalitis / myelitis (including transverse myelitis), Bell's palsy, optic neuritis, and brachial neuritis.
• Staff contact subjects by telephone at D180 post-vaccination to review the memory aid and to identify the occurrence of any SAEs and AESIs that had not yet been reported.
• Interactive response technology (IRT) was used to randomly assign subjects, in each age group, to one of the two vaccine groups and to assign subject numbers in each of the groups.
• Electronic data capture is used for the collection of data.

Safety findings within 28 days of vaccination. Safety analysis were performed on the SafAS, which consisted of a total of 1,533 subjects.

In the over 65 years old subgroup, which is pertinent to the approved indication, injection site reactions and systemic solicited reactions were reported with higher rates by the subjects who received QIV-HD vs the subjects who received QIV-SD (49.4% vs 28.3 % and 34.6% vs 26.2 %). Rates of unsolicited AEs and adverse reactions (ARs) were also higher in the QIV-HD group vs the QIV-SD group.
The unsolicited non-serious ARs reported for the QIV-HD and QIV-SD groups were found to be similar in adults 60 to 64 years of age and adults 65 years of age and older.
Within 28 days of vaccination, one AE (intervertebral disc protrusion) reported by one subject (60 to 64 years age group) in the QIV-HD group led to withdrawal from the study. This AE was assessed as not related to the study vaccine by the Investigator.
No deaths or AESIs were reported within 28 days of vaccination.
Within 28 days of vaccination, a total of five SAEs were reported by five subjects in the QIV-HD group and five SAEs were reported by five subjects in the QIV-SD group.
SAEs reported were acute myocardial infarction (16 hours 55 minutes after receipt of vaccine) pilonidal cyst, cerebral thrombosis, transient ischaemic attack, and exacerbation of intermittent

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claudication in the QIV-HD group. The pilonidal case in the QIV-HD group and coronary artery stenosis and nephrolithiasis in the QIV-SD group were reported in subjects 60-64 years of age. Coronary artery stenosis, intestinal occlusion, rectal bleeding, polycythaemia vera, and nephrolithiasis were reported in the QIV-SD group. None were considered to be related to the vaccine by the investigator. None of the SAEs led to study discontinuation.

As a post-authorisation requirement, six-month follow-up data will be submitted to allow further assessment of SAEs, deaths and AESIs.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Influenza vaccination is the cornerstone public health intervention to reduce the annual burden of influenza epidemics. Vaccination, especially for risk groups that have a higher chance of experiencing complications or more severe influenza disease, is recommended by several medical organisations, societies, and national immunisation technical advisory groups in order to reduce the influenza-associated morbidity and mortality.
The burden of influenza infection and complications is the highest in older adults over 65 years. “Approximately 90% of influenza-related deaths and 50-70% of influenza-related hospitalisations occur among people in this age group in the US. Because of their increased risk, older adults are a priority group for vaccination.”[2]

In support of this current application, the company submitted a comprehensive dossier. Two studies were considered pivotal for the application.
Study FIM12 evaluated the efficacy of the TIV-HD relative to standard-dose TIV regarding any PCR/culture-proven protocol defined ILI in the elderly. The primary endpoint for demonstrating superiority with the per protocol ILI definition was fulfilled with 24.24% (95% CI 9.69; 36.52) combined over 2 years, as the lower boundary of of the 95% CI exceeded the pre-defined threshold of 9.1%.

The other pivotal study, **QHD00013,** was intended to bridge the QIV-HD to the TIV-HD by demonstrating comparable immunogenicity and safety profiles. Study QHD00013 met its primary objectives, demonstrating that QIV-HD was non-inferior to TIV-HD1 and TIV-HD2 as assessed by the HAI GMTs and seroconversion rates for all four strains on day 28 post-vaccination.
The seroprotection rates were high for all strains at 28 days after vaccine administration for the QIV-HD vaccine, ranging from 95.1-99.3%.
Study QHD00013 reached its endpoints for making the immunological bridging possible and allowed the efficacy data obtained with the TIV-HD vaccine to be inferred to the QIV-HD.
In Study QHD00013, one of the pivotal studies supporting this application, QIV-HD demonstrated non-inferior immunogenicity for all four strains as assessed by the GMTs and seroconversion at 28 days post-vaccination compared to TIV-HD. In case of the A strains, comparison was made to the pooled data of the two TIV-HDs containing one of the B types and, in case of the B strains to the TIV-HD with the corresponding B type.
For the two B strains, superiority as assessed by the GMTs and seroconversion rates could be demonstrated compared to the vaccines with the alternate B type. The seroprotection rates were similar for the vaccine groups for all strains. These results of Study QHD00013 demonstrated that the immunogenicity of the QIV-HD vs TIV-HD is comparable, and that the additional B type does not interfere with the immune response of the other strains in a mostly pre-vaccinated elderly population.

As well as demonstrating comparable immunogenicity of the QIV-HD to the TIV-HD vaccines, Study QHD00013 was intended to provide immunological bridging to the TIV-HD.
Vaccines used in the pivotal efficacy study performed with the TIV-HD vaccine (FIM12) was conducted with vaccines manufactured with the legacy process and the control vaccine in Study QHD00013 with the current process.

[2] https://www.cdc.gov/flu/spotlights/2018-2019/hopitalization-rates-older.html

Comparability of the vaccine products has been evaluated by quality attributes, although it would have been preferable to demonstrate the comparability by clinical studies.

With its answer to the Preliminary Decision, the company submitted results from Study QHD00011 assessing the immunogenicity and safety of QIV-HD to a standard dose quadrivalent influenza vaccine approved in Switzerland.

The submission did not provide data on clinical efficacy or effectiveness data specific to the QIV-HD. Furthermore, data on the co-administration of the QIV-HD or the TIV-HD with other vaccines were not available.

Subjects in Study FIM05 who received TIV-HD had higher rates of solicited reactions compared to subjects who received standard-dose TIV, which was mostly driven by the higher rates of solicited injection site reactions.
TIV-HD was non-inferior to standard Fluzone for the systemic reactions of headache, malaise, and myalgia, and was inferior for “moderate or severe” fever.
In Study QHD00013, no new safety concerns were identified for QIV-HD compared to TIV-HD, although a slightly greater reactogenicity was observed with the QIV-HD. This could be explained by the higher amounts of HA and impurities. No imbalances in the frequency or severity of unsolicited adverse events were observed between the groups, and serious or uncommon conditions were not observed at unexpectedly high frequencies in any group.
In Study QHD00011, injection site reactions and systemic solicited reactions were reported at higher rates by the subjects who received QIV-HD vs the subjects who received QIV-SD, and the rates of unsolicited AEs and ARs were also numerically higher in the QIV-HD group vs the QIV-SD group.
Six-month safety data are still missing, as data collection was still ongoing at the time of submission of the response to the Preliminary Decision.
The information for healthcare professionals and the RMP were updated with the data based on the results of the study. The company confirmed the implementation of the annual "Enhanced safety surveillance" (EPSS) activities and committed to submit a PSUR/PBRER annually. Additionally, the final clinical study report for QHD00011 is the subject of a post authorisation requirement.

The safety profile of Efluelda is adequate, and the higher reactogenicity compared to the standard-dose quadrivalent influenza vaccine and also to the TIV-HD can be accepted.

Overall, the benefit/risk for Efluelda for adults over 65 years of age with the approved indication is considered to be positive based on the submitted data.
In the absence of specific efficacy studies with Efluelda, non-inferior immunogenicity results demonstrated comparability with the TIV-HD. This immunobridging of the QIV-HD to the TIV-HD allowed the efficacy results demonstrated for the TIV-HD to be applied to Efluelda.
The additionally submitted QHD00011 study provided further relevant confirmatory information on the immunogenicity and safety of Efluelda compared to a standard-dose quadrivalent influenza vaccine.
As a post-authorisation requirement the final study report for Study QHD00011, including the six-month follow-up safety data, will be submitted to allow further assessment of SAEs, deaths and AESIs.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Efluelda, suspension for injection in pre-filled syringe was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼

NAME OF THE MEDICINAL PRODUCT

EFLUELDA, suspension for injection in pre-filled syringe
Quadrivalent influenza vaccine (split virion, inactivated) High-Dose

Composition

Active substances

Influenza virus strains* (inactivated, split) of type A (H1N1), A (H3N2), B (Yamagata) and B (Victoria) according to annual recommendation of the WHO for the northern hemisphere.

* propagated in embryonated chicken eggs

EFLUELDA may contain traces of eggs, such as ovalbumin, as well asformaldehyde, which are used during the manufacturing process.

Excipients

Sodium-phosphate-buffered isotonic sodium chloride solution (sodium chloride, monobasic sodium phosphate, dibasic sodium phosphate, water for injection), Octoxinol-9.
This medicinal product contains 2.72 mg sodium per dose.

Pharmaceutical form and active substance quantity per unit

Suspension for injection, in a pre-filled syringe.
One dose (0,7 ml) contains 60 μg haemagglutinin of each of the four influenza virus strains.
EFLUELDA, after shaking gently, is a colourless opalescent liquid.

Indications/Uses

EFLUELDA is used for active immunization of adults aged 65 years and older for prophylaxis of influenza caused by the two influenza A virus subtypes and the two influenza B virus subtypes contained in the vaccine.

EFLUELDA must be used in accordance with the official vaccination recommendations.

Dosage/Administration

To ensure the traceability of biotechnological medicinal products, it is recommended that the trade name and the batch number should be documented for each treatment.
In adults 65 years of age and older: one dose of 0.7 ml.

Adult from 18 to 64 years of age
The safety and effectiveness of EFLUELDA have not been established in adults 18 to 64 years of age.
EFLUELDA is not indicated in adults 18 to 64 years of age.

Children and adolescents

The safety and effectiveness of EFLUELDA in children less than 18 years of age have not been established.
EFLUELDA is not indicated in children under 18 years of age.

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 “Instructions for handling”.

Contraindications

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

Warnings and precautions

Before vaccination, the medical history must be checked (in particular with regard to previous vaccinations and any undesirable effects).
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 shall be postponed in patients with moderate or severe acute disease with ot without fever.

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.
A syncope (fainting), sometimes associated with falls, can occur after or even before each vaccination, as a psychogenic reaction to the needle injection. It can be accompanied during the recovery phase by various neurological symptoms such as temporary visual disturbance, paresthesia and tonic-clonic movements of the limbs. Suitable precautions must be taken to prevent injuries due to fainting and to treat syncope.
EFLUELDA is designed to protect against the strains of influenza virus from which the vaccine is produced.
Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.
As with any vaccine, a protective immune 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”.

Interactions

No interaction studies have been performed, nor data to assess the concomitant administration of EFLUELDA with other vaccines.
If EFLUELDA needs to be given at the same time as another injectable vaccine(s), immunisation should be carried out on separate limbs.
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.

Pregnancy, lactation

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

Pregnancy

Animal reproductive studies have not been conducted with EFLUELDA. It is also not known whether EFLUELDA can cause foetal harm when administered to a pregnant woman.
Data on the use of influenza high dose vaccine in pregnant women are not sufficiently available. Pregnant women should be vaccinated with standard dose influenza vaccines, as there is considerably more data available for use in pregnancy (see “Indications/Uses”).

Lactation

It is not known whether EFLUELDA is excreted in human milk. EFLUELDA should not be used on breast-feeding women (see “Indications/Uses”).

Fertility

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

Effects on ability to drive and use machines

EFLUELDA has no or negligible influence on the ability to drive and use machines. Some of the events observed under undesirable effects, such as headaches, fever or drowsiness, can have an influence on the ability to drive or use machines.

Undesirable effects

Adverse event information is based on data coming from two clinical trials with EFLUELDA and on the post-marketing experience of Trivalent Influenza Vaccine (Split Virion, Inactivated) High-Dose.
The safety of EFLUELDA was assessed in a pooled analysis of two clinical trials (QHD00013 and QHD00011) in which 2171 adults over 65 years of age received one dose (0.7 mL) of EFLUELDA. For all subjects, safety evaluations were performed during the first 28 days following vaccination. In the study QHD00013, serious adverse reactions were collected during six months of follow-up.

The most common reactions occurring after EFLUELDA administration were injection site pain (41.0 %), myalgia (22.5 %), headache (15.0 %) and malaise (14.1 %). The majority of these reactions occurred and resolved within three days of vaccination.
Reactogenicity of EFLUELDA containing 60 micrograms haemagglutinin of each virus strain per dose was increased as compared to the standard dose vaccine.

The data below summarizes the frequencies of adverse reactions that were recorded following vaccination with EFLUELDA during QHD00013 and QHD00011 clinical trials (2171 adults 65 years of age and older) and adverse reactions reported during clinical development and post-marketing experience with Trivalent Influenza Vaccine (Split Virion, Inactivated) High-Dose (marked with * 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).

General Disorders and Administration Site Conditions
Very common: Injection site pain (41.0 %), malaise (14.1 %)
Common: Injection site: erythema, swelling, induration, bruising; shivering
Uncommon: Fever (≥ 37.5 °C), injection site pruritis, fatigue
Not known*: Chest pain

Musculoskeletal and Connective Tissue Disorders
Very common: Myalgia (22.5 %)
Uncommon: Muscle weakness[a]
Rare: Arthralgia, Pain in extremities

Nervous System Disorders
Very common: Headache (15.0 %)
Uncommon:Lethargy[a]
Rare: Dizziness, paraesthesia
Not known*: 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)

Blood and Lymphatic System Disorders
Not known*: Thrombocytopenia, lymphadenopathy

Respiratory, Thoracic and Mediastinal Disorders
Uncommon: Cough
Rare: Oropharyngeal pain, Rhinorrhea
Not known*: Dyspnea, wheezing, throat tightness

Gastrointestinal Disorders

Uncommon: Diarrhoea, vomiting dyspepsia[a]

Rare: Nausea

Skin and subcutaneous tissue disorders

Not known*: Stevens-Johnson syndrome

Immune System Disorders

Rare: Pruritus, urticaria, night sweats, rash

Not known*: Anaphylaxis, other allergic/hypersensitivity reactions (including angioedema)

Vascular Disorders

Rare: Flushing

Not known*: vasculitis, vasodilatation

Ear and Labyrinth Disorders

Rare: Vertigo

Eye Disorders

Rare: Ocular hyperemia

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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

Overdose

Cases of administration of more than the recommended dose have been reported with Trivalent Influenza Vaccine (Split Virion, Inactivated) High-Dose 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 Trivalent Influenza Vaccine (Split Virion, Inactivated) High-Dose.

Properties/Effects

ATC code

J07BB02

Mechanism of action

EFLUELDA actively immunises the four strains of influenza contained in the vaccine (two A subtypes and two B subtypes).
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.

Pharmacodynamics

EFLUELDA induces humoral antibodies against hemagglutinins within 2 to 3 weeks. These antibodies neutralize influenza viruses.
A correlation of certain titers of hemagglutinin inhibitory (HAI) antibodies after the application of inactivated influenza virus vaccines on the one hand and the protective effect against influenza has not been established, however, the HAI antibody titers are used as a measure of vaccine activity. Some challenge studies in humans show a link between HAI antibodies of ≥ 1 : 40 and a 50 % reduction of risk of influenza illness.

Clinical efficacy

Immunogenicity
The immunogenicity of EFLUELDA was evaluated in two clinical trials (QHD00013 and QHD00011).

Study QHD00013
QHD00013 was a randomized, active-controlled, modified double-blind Phase III clinical trial conducted in the US in adults 65 years and older.

The objective was to demonstrate the noninferiority of EFLUELDA over Trivalent Influenza Vaccine (Split Virion, Inactivated) High-Dose, 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 Trivalent Influenza Vaccine (Split Virion, Inactivated) High-Dose (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 1[a]: 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	QIV-HD	TIV-HD1[d] (B1 Victoria)	TIV-HD2[e] (B2 Yamagata)			Met Pre-defined Noninferiority Criteria[f]
GMT (95% CI)						
	N[c]=1679-1680	**N[c]=423**	**N[c]=430**	**GMT Ratio QIV-HD over TIV-HD (95 % CI)**		
A (H1N1) [g]	312 (292; 332)	374 (341; 411)		0.83 (0.744; 0.932)		Yes
A (H3N2) [g]	563 (525; 603)	594 (540; 653)		0.95 (0.842; 1.066)		Yes
B1 (Victoria)	516 (488; 545)	476 (426; 532)	-	1.08 (0.958; 1.224)		Yes
B2 (Yamagata)	578 (547; 612)	580 (519; 649)	1.00 (0.881; 1.129)	1.00 (0.881; 1.129)		Yes
Seroconversion Rate (Percentage) (95 % CI)[b]						
	N[c]=1668-1669	**N[c]=420-421**	**N[c]=428**	**Difference of Seroconversion Rates QIV-HD minus TIV-HD (95 % CI)**		
A (H1N1) [g]	50.4 (48.0; 52.8)	53.7 (50.2; 57.1)		-3.27 (-7.37; 0.86)		Yes
A (H3N2) [g]	49.8 (47.3; 52.2)	50.5 (47.1; 53.9)		-0.71 (-4.83; 3.42)		Yes
B1 (Victoria)	36.5 (34.2; 38.9)	39.0 (34.3; 43.8)	-	-2.41 (-7.66; 2.70)		Yes
B2 (Yamagata)	46.6 (44.2; 49.0)	-	48.4 (43.5; 53.2)	-1.75 (-7.04; 3.53)		Yes
Seroprotection n (%) ≥ 40 1/dil (95 % CI)						
	N=1680	**N=423**	**N=430**			
A (H1N1) [g]	1598 (95.1) (94.0; 96.1)	820 (96.1) (94.6; 97.3)		-		
A (H3N2) [g]	1627 (96.9) (96.0; 97.7)	826 (96.8) (95.4; 97.9)		-		
B1 (Victoria)	1664 (99.0) (98.5; 99.5)	419 (99.1) (97.6; 99.7)	415 (96.5) (94.3; 98.0)	-		
B2 (Yamagata)	1669 (99.3) (98.8; 99.7)	409 (96.7) (94.5; 98.2)	426 (99.1) (97.6; 99.7)	-		

[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 Trivalent Influenza Vaccine (Split Virion, Inactivated) High-Dose) is >-10%. Predefined noninferiority criterion for the GMT ratio: the lower limit of the 95 % CI of the GMT ratio (EFLUELDA divided by Trivalent Influenza Vaccine (Split Virion, Inactivated) High-Dose) 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.

NA: Not applicable

Moreover, EFLUELDA induced a superior immune response (GMT) with respect to the additional B strain than the immune response induced by Trivalent Influenza Vaccine (Split Virion, Inactivated) High-Dose that does not contain the corresponding B.

QHD00011

A randomized, active-controlled, modified double-blind, Phase III clinical trial was conducted in Europe in adults 60 years and older to compare EFLUELDA with QIV-SD (standard dose quadrivalent influenza vaccine) for all strains, as assessed by hemagglutinin-inhibiting (HAI) GMTs at D28. Immunogenicity results are presented for adults 65 years of age and older (see Table 2).

A total of 779 adults 65 years of age and older were randomized to receive either one dose of EFLUELDA or one dose of QIV-SD.

Table 2: Study 2a: Immunogenicity results according to HAI method in adults aged 65 years and older, 28 days after vaccination. Full Analysis Set

Influenza Strain	Adults 65 years of Age and Older			Met Pre-defined Superiority Criteriad
	GMT		GMT Ratio	
	TRADE-NAME Nb=392 (95 % CI)	QIV-SD Nb=381 (95 % CI)	TRADE-NAME over QIV-SD (95 % CI)	
A (H1N1)	286 (250 ; 326)	162 (139 ; 190)	1.76 (1.44 ; 2.15)	Yes
A (H3N2)	324 (281 ; 374)	151 (129 ; 176)	2.15 (1.74 ; 2.65)	Yes
B1 (Victoria)	405 (366 ; 447)	262 (236 ; 291)	1.55 (1.34 ; 1.79)	Yes
B2 (Yamagata)	536 (485 ; 592)	305 (274 ; 340)	1.76 (1.52 ; 2.03)	Yes
Seroconversion Rate[c] (Percentage) (95 % CI)				
A (H1N1)	57.9 (52.8 ; 62.8) N=392	37.0 (32.1 ; 42.1) N=381	-	
A (H3N2)	87.0 (83.2 ; 90.1) N=391	71.8 (67.0 ; 76.3) N=380	-	
B1 (Victoria)	56.9 (51.8 ; 61.9) N=390	34.7 (30.0 ; 39.8) N=380	-	
B2 (Yamagata)	55.2 (50.1 ; 60.2) N=388	34.7 (30.0 ; 39.8) N=380	-	
Seroprotection Rate n (%) ≥ 40 1/dil (95 % KI)				
A (H1N1)	95.2 (92.5 ; 97.1) N=392	84.5 (80.5 ; 88.0) N=381	-	
A (H3N2)	92.6 (89.5 ; 95.0) N=392	83.7 (79.6 ; 87.3) N=381	-	
B1 (Victoria)	99.0 (97.4 ; 99.7) **N=392**	99.0 (97.3 ; 99.7) **N=381**	-	

B2 (Yamagata)	99.2 (97.8 ; 99.8) **N=392**	97.1 (94.9 ; 98.6) **N=381**	-	

[a] NCT04024228

[b] N is the number of participants with available data for the considered endpoint

[c] Seroconversion rates: For study participants with a titer of < 10 (1/dil) before vaccination, the proportion of participants with a titer of ≥ 40 (1/dil) after vaccination, and for study participants with a titer of ≥ 10 (1/dil) before vaccination, the proportion of participants in whom the titer increased at least fourfold after vaccination compared with the value before.[d] Fixed superiority criterion: The lower limit of the two-sided 95% CI of the ratio of GMT between groups (QIV-HD/QIV-SD) was > 1 for each strain and in each age group.

Clinical efficacy

No data are available on the clinical efficacy of EFLUELDA.

The Clinical Efficacy of the trivalent high dose influenza vaccine was studied in the FIM12 study.

FIM12 was a multi-centre, modified 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 Trivalent Influenza Vaccine (Split Virion, Inactivated) High-Dose 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), defined as the occurrence of at least one of the following respiratory symptoms: sore throat, coughing, sputum production, wheezing or shortness of breath; accompanied by at least one of the following systemic signs or symptoms: body temperature > 37.2 °C, chills, fatigue, headache or myalgia, 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.

Table 3: **Relative vaccine efficacy against laboratory-confirmed Influenza regardless of similarity to the vaccine components, associated with Influenza-Like Illness in adults ≥ 65 years**

	High Dose trivalent vaccine N[a]=15892 n[b] (%)	**Standard dose trivalent vaccine N[a]=15911 n[b] (%)**	**Relative Efficacy % (95 % CI)[d]**
Laboratory-confirmed influenza[c] caused by:			
- **Any type/subtype**	227 (1.43)	300 (1.89)	24.2 (9.7; 36.5)

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

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

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

[d]The pre-established statistical superiority criterion for the primary endpoint (lower limit of the bilateral 95 % CI of vaccine efficacy for the high-dose vaccine compared to the standard dose is > 9.1 %) was met.

Pharmacokinetics

Absorption

Not applicable

Distribution

Not applicable

Metabolism

Not applicable

Elimination

Not applicable

Preclinical 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.

Other information

Incompatibilities

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

Shelf life

12 months
Do not use this medicine after the expiry date ("EXP") stated on the container.

Special precautions for storage

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

Instructions for 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.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

67704

Packs

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 (B).
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 (B).

Marketing authorisation holder

sanofi-aventis (suisse) sa, 1214 Vernier

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March 2021