COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Efluelda
suspension for injection in pre-filled syringe (trivalent influenza vaccine [split virion, inactivated], 60 micrograms HA/strain)

NL/H/6089/001/DC

Date: 11 February 2025

This module reflects the scientific discussion for the approval of Efluelda suspension for injection in pre-filled syringe. The procedure was finalised on 24 October 2024. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
HA	Hemagglutinin
HD	High Dose
ICH	International Conference of Harmonisation
IPC	In-Process Control
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
QIV	Quadrivalent Influenza Vaccine
QIV-HD	Quadrivalent Influenza Vaccine-High Dose
QIV-SD	Quadrivalent Influenza Vaccine-Standard Dose
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SD	Standard Dose
SIRD	Single Radial Immunodiffusion
SmPC	Summary of Product Characteristics
TIV	Trivalent Influenza Vaccine
TIV-HD	Trivalent Influenza Vaccine-High Dose
TIV-SD	Trivalent Influenza Vaccine-Standard-Dose
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Efluelda, suspension for injection in pre-filled syringe from Sanofi Winthrop Industrie.

The product 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.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

This decentralised procedure concerns an application for a marketing authorisation for high-dose trivalent inactivated influenza vaccine. The marketing authorisation has been granted pursuant to Article 8(3) (full or full-mixed application (complete dossier)) of Directive 2001/83/EC. It concerns a full application including quality, pre-clinical and clinical data, where the studies conducted by the MAH are supplemented with bibliographical data.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, and Sweden.

The WHO recommendation to exclude the B/Yamagata strain from quadrivalent influenza vaccines (QIV) led to the new application of Efluelda trivalent influenza vaccine (TIV). This application is largely based on the dossier of Efluelda Tetra Quadrivalent influenza vaccine (NL/H/4757/001/DC) with the following clinical data package:

Clinical data generated with trivalent influenza vaccine-high dose (TIV-HD) in persons 65 years of age and older in order to demonstrate:

- High dose of hemagglutinin (HA) (60 µg per strain) improved immunogenicity of influenza vaccine, with an acceptable safety profile (Study FIM01)
- Superior immune responses compared with trivalent influenza vaccine-standard dose (TIV-SD) (15 µg of HA per strain) (Study FIM05)
- Improved protection against influenza compared with TIV-SD (Study FIM12) as well as clinical study effectiveness and real-world evidence (RWE) data
- Tolerance of TIV-HD based on Study FIM05. Serious adverse events (SAEs) were also analysed in Studies FIM01, FIM05, FIM12, and FIM07

Clinical data to demonstrate non-inferior immunogenicity and similar safety profile of quadrivalent influenza vaccine-high dose (QIV-HD) compared with TIV-HD in adults 65 years of age and older (Study QHD00013; bridging of the TIV-HD clinical dossier to the QIV-HD vaccine).

For Efluelda Tetra within the variation of NL/H/4757/001/DC an indication extension was granted of persons of 65 years of age and older, to persons of 60 years of age and older based on study QHD00011. This study was a Phase III, randomized, modified double-blind, active-controlled, multicenter study conducted in approximately 1540 healthy adults (770 adults 60 to 64 years of age and 770 adults 65 years of age and older). The primary objective was to demonstrate QIV-HD induces an immune response that is superior to the responses induced by quadrivalent influenza vaccine-standard dose (QIV-SD) for all four virus strains 28 days post-vaccination in subjects 60 to 64 years of age and in subjects 65 years of age and older.

Paediatric Development
The Paediatric Investigational Plan was adopted in 2018 with EMEA-002353-PIP01-18.

- A waiver was granted for the paediatric population from birth 18 years of age on the grounds that the specific medicinal product does not represent a significant therapeutic benefit.

This PIP waiver is applicable.

II. QUALITY ASPECTS

II.1 Introduction

Efluelda is a suspension for injection in a pre-filled syringe. After shaking gently, Efluelda is a colourless opalescent liquid. It contains trivalent influenza vaccine (split virion, inactivated), 60 micrograms HA/strain. One dose contains 0.5 mL.

The vaccine contains influenza virus (inactivated, split) of the following strains* per 0.5 mL dose:

- 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**

* propagated in embryonated chicken eggs

** haemagglutinin

The excipients are: sodium phosphate-buffered isotonic sodium chloride solution: sodium chloride, monobasic sodium phosphate, dibasic sodium phosphate, water for injection; and octoxinol-9.

Efluelda may contain traces of eggs, such as ovalbumin, formaldehyde which are used during the manufacturing process.

0.5 mL of suspension for injection is packed in a pre-filled syringe (Type I glass) equipped with a plunger stopper (bromobutyl rubber) and a tip-cap. Pre-filled syringe(s) are provided either without needle(s), with separate needle(s) (stainless steel) or with separate needle(s) (stainless steel) with safety shield (polycarbonate).

II.2 Drug Substance

The influenza Drug Substance consists of inactivated split viral particles prepared from influenza viruses propagated in embryonated chicken eggs. The final trivalent bulk is formulated with three influenza strains (one strain A H1N1, one strain A H3N3 and strain B).

Manufacturing process

The manufacturing development has been described in sufficient detail. The manufacturing operation uses embryonated chicken eggs to produce monovalent concentrate (drug substance). The harvest fluid (egg allantoic fluid) that contains influenza virus is inactivated, purified, disrupted, concentrated and sterile filtered to produce drug substance. Released monovalent concentrates of the same strains combined (pooled) to form a monovalent pool, are used to formulate the final bulk drug product. Comparability of the QIV-HD batches manufactured according the current manufacturing process to clinical batches has been sufficiently demonstrated.

Quality control of drug substance

The specifications of the drug substance are acceptable and in line with current compendial requirements and other regulatory/scientific expectations. Many assays are pharmacopoeia tests and have been validated for the matrix, including identity, sterility testing, virus inactivation testing, pH, and endotoxin content. All of these pharmacopoeia tests were appropriately qualified for their use in testing of TIV-HD. Batch results of several development stages are provided and specifications are met across all different stages of development and across the different influenza A and B strains. Single Radial Immunodiffusion (SIRD) assay is validated for each strain as part of the annual strain update.

Stability of drug substance

All long-term stability study results meet the acceptance criteria for nine lots of influenza drug substance when stored at 1°C to 5°C (long-term conditions). No acceptance criteria were applied to the samples stored at the accelerated condition (23°C to 27°C). Overall, the presented stability data support the claimed maximum holding time of 24 months for the drug substance when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The TIV-HD is a sterile suspension of the three strains (two A strains and one B strain) prepared from influenza viruses propagated in embryonated chicken eggs. TIV-HD vaccine is formulated to contain 180 µg HA per 0.5 mL dose, in the ratio of 60 µg HA of each strain, representative of the three prototype strains. It also contains Triton X-100 which is claimed to stabilise/preserve the vaccine antigens.

The vaccine development and validation is based on Efluelda Tetra (QIV-HD). In general, sufficient detailed information is provided about the pharmaceutical and manufacturing process development in support of the commercial TIV-HD manufacturing. Due to the decrease in fill weight (0.7 mL to 0.5mL), a larger amount of syringes can be filled from one final bulk batch. However, during process validation, a smaller batch was produced. The technical assessment justifies that the amended batch size will generate longer filling duration, which is covered by the current aseptic process simulation. The implementation will not modify aseptic practices and therefore does not entail a risk with regard to microbiological tests and endotoxin content conducted on the product.

Manufacturing process

The manufacturing process is a straightforward process comprising mixing of drug substance and buffer (with Triton X-100 if required), filtration, and filling into containers.

Sufficient controls (process parameters, in-process control (IPC)) are established. The MAH committed to implement pre-filtration bioburden testing acceptance limit at the manufacturing sites, in line with the Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container (EMA/CHMP/CVMP/QWP/850374/2015). Process validation has been performed and justified for both the formulation and filling process steps. It is acknowledged that the manufacturer has experience with the licensed products from their Influenza vaccine drug product family and therefore revalidation of specific steps for the TIV-HD formulation is not necessarily required if justified.

Control of excipients

The control of excipients is taken over from the QIV-HD drug product dossier without adaptations. These specifications are acceptable.

Triton X-100 is a non-compendial excipient. The release specifications for Triton X-100 are provided and considered acceptable.

Closure systems/containers for Final Bulk Product and Filled Product

Release specifications are provided for Final Bulk Product and Final container and are compliant with Ph. Eur 0158. In general, the analytical procedures for batch release and their validation are satisfactorily described. Details on the closure systems/containers for Final Bulk Product and Filled Product are provided, including information on the container components, potential leachables and closure integrity testing results. Further justification that the submitted data for QIV-HD are applicable for Efluelda TIV-HD is provided in the technical assessment report. Leachable testing was performed. No leachables were detected in product extracts above the limits for any of the procedures employed in the filter validation studies. These analytical testing limits along with the safety concern threshold determined the minimum batch size per filter to ensure leachables remain below the threshold.

Microbiological attributes

The medicinal product is sterile with no preservatives added. Furthermore, TIV-HD is tested for sterility prior to release of the product. Container closure integrity to prevent microbial contamination is supported by the stability study sterility tests and pharmaceutical

development studies. The aseptic filling process has been validated. In addition, every final bulk product is sampled and tested for bioburden content pre-filtration and for sterility at release. For filling, the final formulated bulk vessel is attached to the filling line by means of aseptic connections, pre-sterilized disposable assemblies, and sterilized equipment.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The final bulk product specification includes tests for sterility, virus inactivation, endotoxin content, HA, Triton X-100, pH, formaldehyde, protein and ovalbumin. The filled product specification includes tests for sterility, pH, extractable volume, appearance, identity and hemagglutinin antigen content and endotoxin content. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data of the 2017/2018 QIV-HD batches (five final bulk, five filled container and three labelled product batches) was provided. The corresponding TIV-HD batch analysis data and additional data from the clinical batches manufactured for the 2019/2020 Northern Hemisphere (NH) was provided as support. Additionally, data for batches manufactured for NH 2020/2021 is presented to support the QIV-HD Final Bulk Scale Up variation. Batch result specifications were met.

Stability of drug product

Stability data on the product have been provided for nine batches stored at 1°C - 5°C for final bulk or 2°C - 8°C for final container (syringe) (12 months) and 23°C - 27°C (6 months) in accordance with applicable European guidelines. On basis of the data submitted, a shelf life was granted of 12 months. The labelled storage conditions are “Store in a refrigerator (2 °C – 8 °C). Do not freeze. Keep the syringe in the outer carton in order to protect from light.”

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The MAH declared that the prefilled syringe that is used for the TIV-HD vaccine is the same as for the QIV-HD vaccine. Therefore, there are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Efluelda has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The MAH committed to implement the pre-filtration bioburden testing acceptance limit of 10CFU/100 mL at the manufacturer site via a variation prior to the NH 2026/2027 campaign.
- The MAH committed to harmonize the acceptance criteria for glide force between manufacturer site I and site II by 3Q 2026.
- The MAH committed to produce future monovalent concentrate pools using monovalent concentrates aged not more than those included in the stability study conducted in 2019 (S2019-008). These monovalent concentrates would not be older than eight months from date of production.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Pharmacology studies were not performed with TIV-HD or QIV-HD. Considering the clinical experience with the influenza vaccine and the fact that the strains in the vaccine are recommended by the WHO, additional non-clinical studies to demonstrate the efficacy of the vaccine are not necessary. The additional advantage of the higher dose of antigen will have to be demonstrated clinically.

Studies on secondary pharmacodynamics, safety pharmacology and pharmacodynamics drug interactions have not been performed. In accordance with the Guideline on Influenza Vaccines (EMA/CHMP/VWP/457259/2014), these studies are considered not necessary.

III.2 Pharmacokinetics

Pharmacokinetics studies have not been performed with TIV-HD or QIV-HD. According to the Guideline on Influenza Vaccines (EMA/CHMP/VWP/457259/2014), studies to determine serum concentrations of antigens are not needed.

III.3 Toxicology

A repeat-dose toxicity study and a local tolerance study with QIV-HD were performed, both in New-Zealand White rabbits.

In the repeat-dose study, rabbits received three intramuscular injections at two-week intervals with the human dose of QIV-HD. Injection site findings and an increase in the number of germinal centers in the spleen were observed as can be expected after intramuscular injection of a vaccine. After three doses, moderate inflammation and/or necrosis to muscle fibers were observed in some animals. This is not considered clinically relevant because only one dose per year is recommended in the SmPC. After one and two injections, necrosis at the injection site was minimal and inflammation was minimal to slight.

In the local tolerance study, rabbits received one human subcutaneous dose of QIV-HD. Only minimal to slight dermal inflammatory changes were observed at the injection site.

Genotoxicity and carcinogenicity studies were not included in the dossier because these studies are not required for influenza vaccines. Reproductive toxicity studies were not performed because the intended target population is 65 years and older. Also, considering the current knowledge regarding the use of influenza vaccines during pregnancy, it is not necessary to perform a reproductive toxicity study.

The total of worst-case exposure levels to leachables that were identified in the final container syringe presentation, did not exceed the acceptable total daily intake for multiple impurities according to ICH guideline M7.

III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Efluelda contains inactivated, split virion, it is unlikely to result in a significant risk to the environment. An environmental risk assessment was therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

In line with the Note for Guidance on "the Clinical Evaluation of New Vaccines", pharmacokinetic studies are not considered to provide any additional relevant information for this inactivated split virion influenza vaccine.

IV.2 Pharmacodynamics

There are no dedicated PK studies. This can be accepted as the PK is not considered informative towards the determination of an optimal dose. The metabolic pathways of vaccines are generally understood. Therefore PK studies are generally not required for vaccines.

Immunogenicity, as a surrogate measure for efficacy, determined by a validated HI assay, was assessed in all QIV-HD and TIV-HD clinical studies included in the application and is described in detail in the sections on clinical efficacy. Assessment of neutralisation test and neuraminidase activity was also performed. The use of serological surrogates as an approximation for vaccine efficacy is generally recognized by regulatory authorities including the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) (CHMP/VWP/457259/2014).

IV.3 Clinical efficacy

In support of the current application for the TIV-HD vaccine for the indication of prevention of influenza in adults aged 60 and older the MAH submitted a comprehensive data package.

Pivotal to this application is study FIM12 which evaluated the superiority of TIV-HD (60 µg HA per strain) over TIV-SD (15 µg HA per strain) in preventing laboratory confirmed influenza associated with influenza like illness in adults aged 65 years of age and older.

Study FIM12 demonstrated superiority of TIV-HD as compared to a standard dose TIV in providing protection against laboratory-confirmed influenza caused by any viral types/subtypes (regardless of similarity to those contained in the vaccine) for both study years combined, with a relative vaccine effectiveness of 24.24% (95% CI 9.69; 36.52).

Supportive evidence comes from several studies, including study QHD00011, QHD00028 and QHD00013:

Study QHD00011 was designed to demonstrate the superiority of the immune response of QIV-HD versus QIV-SD in subjects 60 - 64 years of age and 65 years of age and above with regard to the post vaccination geometric mean titer ratio for all four strains in both age groups on Day 28. A superior immune response for QIV-HD was demonstrated. Further, study QHD00011 showed that the immune response after vaccination with QIV-HD in subjects aged 60 to 64 years was similar or higher compared to the immune response in subjects 65 years of age and above, with a difference to QIV-SD of similar magnitude as in adults 65 years and above. Therefore it is reasonable to conclude that QIV-HD will be at least as efficacious in persons aged 60 - 64 years as in persons aged 65 years or older.

Study QHD00028 provided evidence that concomitant administration of QIV-HD with a COVID-19 mRNA vaccine, mRNA-1273 (100 µg), resulted in similar responses to COVID-19 mRNA vaccine, as assessed by an anti-spike IgG assay. Further, the descriptive analyses of the HAI response did not point towards significant or relevant interference when QIV-HD is administered together with mRNA-1273.

Study QHD00013 which provides the bridge between the TIV-HD vaccine and the QIV-HD vaccine, through demonstrating non-inferior immunogenicity and similar safety profile of QIV-HD compared with TIV-HD in adults 65 years of age and older, and provided the evidence that results from FIM12 were also relevant to the QIV-HD vaccine, as the response to the QIV-HD vaccine was shown to be non-inferior to TIV-HD vaccines with alternating B strains.

Further, a large cluster randomised trial in a care home setting backed up with several observational, retrospective cohort studies provide evidence sufficient to conclude that the increased protection against confirmed influenza associated with the HD influenza vaccine may also translate into increased protection against complications of influenza such as pneumonia and hospitalisation associated with influenza although the impact may vary per season. Several observational studies spanning 12 influenza seasons further suggest that the improved immunogenicity and efficacy as demonstrated in FIM00012 translates into improved protection against a range of clinically relevant outcomes, although the impact may vary by season.

IV.4 Clinical safety

The TIV-HD safety profile definition proposed in the Product Information is based on data assessed in the pivotal QIV-HD clinical studies (QHD00013 and QHD00011) and on the clinical and post-marketing experience of QIV-HD and TIV-HD. The data for the QIV-HD reactogenicity profile comes from the integrated safety analysis using data from Studies QHD00013 and QHD00011.

The safety profile of TIV-HD and QIV-HD in adults aged 60 years or older is characterised by mostly mild reactogenicity, predominantly pain following vaccination. The frequency of solicited reactions for TIV-HD and QIV-HD was higher than that observed for TIV-SD or QIV-SD. Reactogenicity is self-limiting and can be expected to occur in approximately 40% of recipients. Adverse were generally rare, with very few unsolicited adverse events potentially related to vaccination.

IV.5 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Efluelda.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	None.
Important potential risks	None.
Missing information	None.

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.6 Discussion on the clinical aspects

In context of the WHO recommendation to remove the B/Yamagata lineage antigen from the current quadrivalent influenza vaccines, the MAH has submitted an application for a Trivalent High Dose Influenza vaccine based on its approved Quadrivalent influenza vaccine 60 µg HA/strain (High-Dose) currently licensed in European Union through the DCP NL/H/4757/001/DC. The Efluelda Trivalent High Dose Influenza vaccine is in general compliant with Ph. Eur 0158 Influenza vaccine (split virion, inactivated) and Guideline on Influenza vaccines (EMA/56793/2014 Rev.2). Based on the review of the data on quality, the RMS considers that from a quality perspective, the application for Efluelda, for active immunisation in adults 60 years of age and older for the prevention of influenza disease, is approvable.

Risk management is adequately addressed. The clinical aspects of this product are approvable.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Quadrivalent influenza vaccine (split virion, inactivated), 60 µg, NL/H/4757/001/DC. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Efluelda suspension for injection in pre-filled syringe has a proven chemical-pharmaceutical quality. In context of the WHO recommendation to remove the B/Yamagata lineage antigen from the current quadrivalent influenza vaccines, the MAH submitted an application for a Trivalent High Dose Influenza vaccine based on its approved Quadrivalent influenza vaccine 60 µg HA/strain (High-Dose) currently licensed in European Union through the DCP NL/H/4757/001/DC. The Efluelda Trivalent High Dose Influenza vaccine is in general compliant with Ph. Eur 0158 Influenza vaccine (split virion, inactivated) and Guideline on Influenza vaccines (EMA/56793/2014 Rev.2). Based on the review of the data on quality, the RMS considers that from a quality perspective, the application for Efluelda, for active immunisation in adults 60 years of age and older for the prevention of influenza disease, is approvable.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Efluelda with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 24 October 2024.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
N/A	N/A	N/A	N/A	N/A	N/A