EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 September 2023
EMA/447177/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zoonotic Influenza Vaccine Seqirus

International non-proprietary name: zoonotic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted)

Procedure No. EMEA/H/C/006375/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

DS	Drug substance
DP	Drug product
HA	Haemagglutinin
HPAI A(H5N1)	Highly pathogenic avian influenza virus of type A of subtype H5N1
ICSRs	Individual case safety reports
MAH	Marketing authorisation holder
MA	Marketing authorisation
NA	Neuraminidase
PI	Product information
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant applied for the following indication: Active immunisation against H5 subtype of Influenza A virus.

The present application pertains to the informed consent procedure according to Article 82(1) of Regulation (EC) No 726/2004 aiming to duplicate the existing marketing authorisation for the H5N1 zoonotic vaccine Aflunov (MAH: Seqirus S.r.l.), into a new vaccine named "Zoonotic Influenza Vaccine Seqirus" (Applicant: Seqirus S.r.l.).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 10(c) of Directive 2001/83/EC – relating to informed consent from a marketing authorisation holder for an authorised medicinal product.

The application submitted is composed of administrative information, quality, non-clinical and clinical data with a letter from a MAH (Seqirus S.r.l) allowing the cross reference to relevant quality, non-clinical and/or clinical data.

1.3. Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/150/2009, P/211/2010, P/132/2011, P/0230/2014, P/0057/2017 and P/0249/2018 on the agreement of a paediatric investigation plan (PIP) EMEA-C-000599-PIP01-09-M07. Moreover, the PIP was modified (P/0189/2020).

A positive compliance check (EMEA-C-000599-PIP01-09-M07) was issued by the PDCO, considering that the measures are in compliance with the agreed above mentioned paediatric investigation plan and that the agreed timelines have been respected accordingly.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Maria Grazia Evandri Co-Rapporteur: Jan Mueller-Berghaus

The application was received by the EMA on	25 July 2023
The procedure started on	14 August 2023
The CHMP and PRAC Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 August 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 August 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Zoonotic Influenza Vaccine Seqirus on	14 September 2023

2. Scientific discussion

2.1. Problem statement

The present application pertains to the informed consent procedure according to Article 82(1) of Regulation (EC) No 726/2004 aiming to duplicate the existing marketing authorisation for the H5N1 zoonotic vaccine Aflunov (MAH: Seqirus S.r.l.), into a new vaccine named "Zoonotic Influenza Vaccine Seqirus" (Applicant: Seqirus S.r.l.).

The reason behind the present informed consent application procedure is that Seqirus intends to continue the marketing of the currently authorised Aflunov H5N1 vaccine and, in parallel, to introduce a new H5N8 vaccine targeting a new clade (2.3.4.4b) which has become dominant in various world regions. The risk for occupationally or otherwise exposed groups to avian influenza-infected birds or mammals is assessed as low to moderate. The candidate virus subtype which has the greatest coverage against the avian viruses of concern which are currently of clade 2.3.4.4b is A/Astrakhan/3212/2020 (H5N8) clade 2.3.4.4b.

Therefore, following duplicate license granting, Seqirus intends to introduce a strain modification for the Zoonotic Influenza Vaccine Seqirus in order to target the new clade, while maintaining the same strain for the current Aflunov license.

2.1.1. Disease or condition

H5 subtype influenza virus is the most widely detected avian influenza virus. Since 1996, when the virus was first identified, it has caused numerous disease outbreaks in domestic poultry and wild birds around the world. The highly pathogenic avian influenza virus of type A subtype H5N1 (HPAI) A(H5N1), that causes high mortality in infected chicken, is the causative agent of H5N1 flu, commonly known as avian influenza ("bird flu").

H5N1 is highly contagious among birds and has a near 100% case fatality rate. It is spread through birds' droppings, saliva, or through contaminated food and water. Recently, there have been a rising number of cases of bird flu detected among mammals. Although human infection is rare (sporadic infection), there is some evidence of limited human-to-human transmission of the virus. Individuals with close contact to birds, including poultry farm workers, are at increased risk of acquiring the infection. Around 60% of humans known to have been infected with the HPAI A(H5N1) have died from it. Further, due to long-term circulation and increasingly large host reservoir, H5N1 may mutate or reassort into a strain capable of efficient human-to-human transmission. According to the WHO, H5N1 pathogenicity is gradually continuing to rise in endemic areas, and due to its high lethality and virulence, and its significant ongoing mutations, the H5N1 virus is regarded to be the largest threat for a potential influenza pandemic.

2.1.2. Epidemiology

In 1996, HPAI A(H5N1) virus is first identified in domestic waterfowl in Southern China. The virus is named A/goose/Guangdong/1/1996. Detections of HPAIV were initially reported in the Far East, and later, in parts of Europe, the Middle East, Africa and the United States.

In 1997, Hong Kong identified the first human infections. In 2003, the first confirmed human cases were notified by WHO, and since then more human cases and fatalities have been reported by WHO.

According to WHO Globally, from January 2003 to 31 May 2023, 876 cases of human infection with avian influenza A(H5N1) virus were reported from 23 countries. Of these 876 cases, 458 were fatal (Case Fatality Rate of 52%). In December 2021, a mild A(H5N1) infection in a person above 75 years of age that had close exposure to infected ducks was reported from the United Kingdom (https://www.ecdc.europa.eu/en/zoonotic-influenza/facts/factsheet-h5n1).

2.1.3. Clinical presentation, diagnosis

In general, humans who catch a humanized influenza A virus (a human flu virus of type A) usually have symptoms that include fever, cough, sore throat, muscle aches, conjunctivitis, and, in severe cases, breathing problems and viral pneumonia that may be fatal. Influenza A virus H5N1 can trigger a 'cytokine storm' by inducing higher levels of cytokines than the more common flu virus types. While it is expected that immunocompromised individuals may develop more severe disease, clinical picture of infection with a humanized H5N1 flu is not yet known.

The reported mortality rate of highly pathogenic H5N1 avian influenza in a human is high and according to WHO reaches 60% of cases. However, there is some uncertainty as people with milder symptoms may not seek treatment.

2.1.4. Management

Currently, Aflunov is the only H5N1 zoonotic vaccine approved in EU.

WHO has published guidance on the clinical management of human infection with A(H5N1) as well as rapid advice guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus.

Four licensed influenza antiviral agents are available in the EU/EEA: amantadine, rimantadine, zanamivir and oseltamivir. However, current circulating seasonal influenza A viruses are resistant (>99%) to the adamantanes (amantadine and rimantadine). Isolates of influenza A(H5) strains are also widely resistant to the adamantanes. Zanamivir and oseltamivir are included in a class of medicinal products known as influenza neuraminidase inhibitors and are active against both influenza A and B viruses. Baloxavir marboxyl has been authorised in 2021 in the EU/EEA.

HPAI A(H5N1) viruses have so far been reported to be sensitive to neuraminidase inhibitors, even though a few viruses of the Egyptian clade showed resistance.

Controlling the virus' spread is the best defence to prevent spilling from birds over into humans. Current seasonal flu vaccines are not effective against bird flu.

There are several H5N1 pandemic vaccines approved in EU, but the continual mutation of H5N1 renders them of limited use to date: while vaccines can sometimes provide cross-protection against related flu strains, the best protection would be from a vaccine specifically produced for any future pandemic flu virus strain.

2.2. About the product

Like the currently authorised Aflunov vaccine, the duplicate "Zoonotic Influenza Vaccine Seqirus" is a monovalent influenza avian vaccine (surface antigen, inactivated, MF59C.1 adjuvanted). The vaccine contains purified HA and NA surface antigens from the influenza avian virus A/turkey/Turkey/1/2005 (H5N1) like strain (NIBRG-23) clade 2.2.1.

Aflunov was developed to protect against a (closely matched) potential zoonotic influenza viral strain via early vaccination at the start of a pandemic or during pre-pandemic stages (e.g. to reduce mortality against a zoonotic pandemic strain in those countries where infections are occurring). It may also help reducing the chance of the emergence of a reassortant pandemic strain by vaccinating those (e.g., veterinarians, poultry workers, operators involved in the manufacturing of vaccines with pandemic-like strains, laboratory workers) at high risk of infection from both avian and human viruses.

In the event of a zoonotic influenza, the "Zoonotic Influenza Vaccine Seqirus" active substance can be updated accordingly with the circulating zoonotic strain according to WHO indication.

The MF59C.1 adjuvant is an oil-in-water emulsion, composed mainly of squalene that is an intermediate metabolite in the synthesis of cholesterol.

The influenza virus strain is propagated in embryonated chicken eggs.

The vaccine is presented as a suspension for injection in pre-filled syringe containing 7.5 micrograms (expressed in micrograms haemagglutinin)/0.5 ml. Packs of 1 or 10 pre-filled syringes are proposed.

2.3. Quality aspects

The "Zoonotic Influenza Vaccine Seqirus" is submitted as an informed consent application of Aflunov, under Article 10(c) of Directive 2001/83/EC.

Therefore, the present application fully cross-refers to the up-to-date quality data of the original dossier of the zoonotic vaccine Aflunov, as further modified through all the post-approval Aflunov quality changes which have been assessed and authorised to date.

It is noted that, with the exception of antigen composition and dose, Aflunov has a manufacturing process highly comparable (i.e. same technology platform/equipment, same adjuvant) to the Seqirus seasonal vaccines such as the EU authorised quadrivalent vaccine "Fluad Tetra" (aQIV) and the nationally authorised trivalent vaccine "Fluad", licensed in several EU countries through a Mutual Recognition Procedure (MRP). Due to the similarity of the manufacturing process adopted for other Seqirus egg-based, MF59C.1 adjuvanted vaccines, most of the Aflunov variation procedures authorised to date have been supported with quality data relative to highly similar platform products, such as the seasonal vaccine Fluad Tetra.

Being an informed consent application procedure, only Module 1 has been submitted to support the present duplicate license for the "Zoonotic Influenza Vaccine Seqirus".

In particular, within Module 1 the applicant has submitted a declaration stating that the "Zoonotic Influenza Vaccine Seqirus" has the same qualitative and quantitative composition in terms of active substance (Influenza virus surface antigens of strain a/turkey/Turkey/1/2005, H5N1) and the same pharmaceutical form as the currently authorised zoonotic vaccine Aflunov.

Moreover, suitable proof of GMP compliance for all the involved DS/DP manufacturing sites has been provided.

The applicant has also provided confirmation that no new or additional sites than those currently approved for the reference medicinal product Aflunov have been included and committed to ensure the same consistency with the manufacturing sites that will be listed in Module 3 (sections 3.2.P.3.1 and 3.2.S.2.1) once the lifecycle of this part of the dossier will start.

To support the present informed consent application, the applicant has also provided additional documentation requested during validation: QP declaration, TSE compliance declaration and risk summary for presence of nitrosamines, which were acceptable.

2.4. Non-clinical aspects

Zoonotic Influenza Vaccine Seqirus is submitted as an informed consent application of Aflunov under Article 10(c) of Directive 2001/83/EC. The present application cross-refers to the up-to-date non-clinical data of the original dossier of Aflunov, which has been assessed and authorised.

2.4.1. Ecotoxicity/environmental risk assessment

Due to the nature of the product (i.e., a vaccine comprised of proteins in an adjuvanted buffer solution) no ERA studies have been performed, since the product is unlikely to result in a significant risk to the environment.

The active substance is a natural substance (7.5 µg of haemagglutinin antigen) and the adjuvant MF59C.1 consists of squalene (a natural organic compound obtained from shark liver oil) polysorbate 80 and sorbitan trioleate, in a sodium citrate / citric acid buffer.

Influenza vaccine A/turkey/Turkey/1/05 (H5N1) (egg based, surface antigen, inactivated, adjuvanted MF59C.1), is already used in existing marketed products and no significant increase in environmental exposure is anticipated.

2.5. Clinical aspects

Zoonotic Influenza Vaccine Seqirus was submitted as an informed consent application of Aflunov under Article 10(c) of Directive 2001/83/EC.

The present application cross-refers to the up-to-date clinical data of the original dossier of Aflunov, which has been assessed and authorised.

Clinical trials (immunogenicity) have been conducted with either the former A/Vietnam/1194/2004 (H5N1) (clade 1) or the A/turkey/Turkey/1/2005 (H5N1) vaccine strain (clade 2.2.1) currently approved as Aflunov. For this reason, the wording of indication was further amended to avoid reference to only "A/turkey/Turkey/1/2005 (H5N1)" like strain" that is how the current AFLUNOV vaccine is composed of, and replacing with "H5N1 subtype strain" leaving it more open.

2.6. Risk Management Plan

Zoonotic Influenza Vaccine Seqirus is submitted as an informed consent application of Aflunov under Article 10(c) of Directive 2001/83/EC.

An RMP version 4.0 was submitted that is not in line with the latest approved EU-RMP version 4.11 of the cross-referred medicinal product. Since RMP is a common document to Foclivia pandemic vaccine and Aflunov zoonotic vaccine, the applicant should add the cross-referred product in Product Overview as Medicinal products to which the RMP refers and release an updated amended version.

The applicant submitted an updated version 5.1 of the RMP to address such concerns.

The RMP is in line with the approved EU-RMP version 5.0 of the cross-referred medicinal product.

2.6.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Neuritis Convulsions Encephalitis (*encephalomyelitis*) Vasculitis Guillain-Barré Syndrome Demyelination Bell's palsy Immune thrombocytopenia
Missing information	Use in pregnancy and lactation

To address minor discrepancies between the RMP for this procedure and the one for Aflunov, the applicant submitted an updated RMP version 5.1 that is in line with the approved information of the reference product.

2.6.2. Pharmacovigilance plan

Zoonotic Influenza Vaccine Seqirus is submitted as an Informed Consent application of Aflunov under Article 10(c) of Directive 2001/83/EC.

An updated version 5.1 of the RMP was submitted and it is in line with the approved version of the cross-referred medicinal product.

The applicant proposes routine pharmacovigilance activities according to includes management of Individual Case Safety Reports (ICSRs), PSURs, monitoring safety profiles, and safety signal detection and evaluation. This is acceptable.

On-going and planned additional pharmacovigilance activities as proposed by the applicant:

Study (Status)	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Enhanced surveillance of vaccine safety (Planned)	To evaluate safety and reactogenicity in terms of local and systemic adverse reactions in the different age groups	Not applicable	Protocol to be provided once pandemic is declared. Milestones to be confirmed	To be confirmed
Category 3 - Required additional pharmacovigilance activities				
V87_27OB is a postmarketing observational cohort safety study of pandemic influenza A/H5N1* vaccine	To evaluate the safety of pandemic influenza vaccine in pregnant women	Use in pregnancy and lactation	Protocol to be provided once pandemic is declared. Milestones to be confirmed	To be confirmed

(Foclivia®) in pregnant women (Planned)				

** The strain is subject to change to be matched with the next pandemic strain*

2.6.3. Risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern.

Safety concern	Routine risk minimisation activities
Neuritis	Neuritis is described in Section 4.8 Undesirable effects of the Foclivia, Aflunov and Zoonotic Influenza Vaccine Seqirus Summary of Product Characteristics (SmPC) and Section 4 of the Package Leaflet (PL).
Convulsions	Convulsions are described in Section 4.4 Special warning and precautions for use of the Foclivia SmPC and Section 4.8 Undesirable effects of Foclivia, Aflunov and Zoonotic Influenza Vaccine Seqirus SmPC; and Section 2 & 4 of the PL.
Encephalitis (*encephalomyelitis*)	Neurological disorders, such as encephalomyelitis, are described in Section 4.8 Undesirable effects of the Foclivia, Aflunov and Zoonotic Influenza Vaccine Seqirus SmPC; and Section 4 of the PL.
Vasculitis	Vasculitis is described in Section 4.8 Undesirable effects of the Foclivia, Aflunov and Zoonotic Influenza Vaccine Seqirus SmPC; and Section 4 of the PL.
Guillain-Barré syndrome	Guillain-Barré syndrome is described in Section 4.8 Undesirable effects of the Foclivia, Aflunov and Zoonotic Influenza Vaccine Seqirus SmPC and Section 4 of the PL.
Demyelination	None; included as a potential safety concern based on pharmacological class effects
Bell's palsy	None; included as a potential safety concern based on pharmacological class effects
Immune thrombocytopenia	None; included as a potential safety concern based on pharmacological class effects
Use in pregnancy and lactation	Use in pregnancy and use during breast-feeding is described in Section 4.6 of Foclivia, Aflunov and Zoonotic Influenza Vaccine Seqirus SmPC; and Section 2 of the PL.

No additional risk minimisation measures have been proposed.

2.6.4. Conclusion

The CHMP considers that the risk management plan version 5.1 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic safety update reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.8. Product information

The proposed product information for Zoonotic Influenza Vaccine Seqirus is mostly aligned with the latest approved version of the product information of the cross-referred product Aflunov. Minor changes proposed by both the CHMP Rapporteur and EMA Label during the assessment were implemented.

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Aflunov. The bridging report submitted by the applicant has been found acceptable.

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004 (REG), similarly to Aflunov, the "Zoonotic Influenza Vaccine Seqirus" is not included in the additional monitoring list for the following reason: informed consent of a product not included in the additional monitoring list.

3. Benefit-Risk Balance

The application for the "Zoonotic Influenza Vaccine Seqirus" is based on an informed consent on the pharmaceutical, non-clinical and clinical documentation contained in the marketing authorisation of Aflunov, as complemented by administrative and prescribing information.

Taking into account the assessment of data previously undertaken for cross-referred medicinal product Aflunov, the benefit-risk balance for the "Zoonotic Influenza Vaccine Seqirus" is considered positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Zoonotic Influenza Vaccine Seqirus is favourable in the following indication(s):

Active immunisation against H5N1 subtype of Influenza A virus.

This indication is based on immunogenicity data from healthy subjects from the age of 18 years onwards following administration of two doses of the vaccine containing H5N1 subtype strain (see sections 4.4 and 5.1).

Zoonotic Influenza Vaccine Seqirus should be used in accordance with official recommendations.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a

state laboratory or a laboratory designated for that purpose.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.