Public Assessment Report

Scientific discussion

Innoflu (IT)/Fluad (UK)

IT/H/525/001/DC

Applicant: Seqirus S.r.l

Date: 08/01/2019

This module reflects the scientific discussion for the approval of INNOFLU. The procedure was finalised at 19/07/2017 For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

"Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for INNOFLU. The therapeutic indication of INNOFLU is applied for: active immunization against influenza in the elderly (65 years of age and over), especially for those with an increased risk of associated complications. The use of INNOFLU should be based on official recommendations A comprehensive description of the indications and posology is given in the SmPC." "The marketing authorisation has been granted pursuant to to Article 8.3 of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

This application concerns the Marketing Authorisation for the medicinal product adjuvant Trivalent Influenza aTVI - INNOFLU. It is an inactivated influenza virus subunit vaccine formulated with MF59C.1 adjuvant. The vaccine is available as a 0.5 ml single dose sterile suspension for injection, contained in a pre-filled syringe.
The aTIV contains purified haemagglutinin (HA) and neuraminidase (NA) antigens from the surface of each of the three influenza virus strains, types A and B, recommended annually for immunisation by the WHO and CHMP for the Northern Hemisphere.
The influenza virus strains are individually grown in embryonated chicken eggs and inactivated by formaldehyde treatment before purification of the surface antigens and formulation with the MF59C.1 adjuvant into a sterile suspension. The MF59C.1 adjuvant contained in aTIV is an oil-in-water emulsion composed of squalene as the oil phase, together with the surfactants polysorbate 80 and sorbitan trioleate, in citrate buffer.
The potency of the vaccine is expressed as the amount of the HA protein per dose.
The composition of aTIV is the same of Fluad that was first registered in Italy in 1997 for the prophylaxis of influenza in elderly people (65 years of age and over). Since then, it has been approved in 12 European countries through a Mutual Recognition Procedure that concluded on April 23rd 2000.
Since its first registration, the vaccine has obtained approval in 30 countries worldwide (of which 15 are in Europe). The product complies with Ph.Eur. monograph for influenza vaccines, surface antigen, inactivated and includes MF59C. l as adjuvant.
The application is submitted under the legal base of Full Dossier referring to Article 8.3 of Directive 2001/83/EC.
The IT is the Reference Member State, UK is the Concerned Member State and the procedure number is IT/H/0525/01/DC. The submitted documentation in relation to the proposed product is of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory overall quality, non-clinical and clinical overviews have been submitted. They represent an adequate summary of the dossier.
The therapeutic indication of INNOFLU is applied for: active immunization against influenza in the elderly (65 years of age and over), especially for those with an increased risk of associated complications.
The use of INNOFLU should be based on official recommendations.
The posology is a single 0.5 ml dose that should be administered by intramuscular injection into the deltoid muscle. Due to the presence of the adjuvant, the injection should be carried out by using a 1 inch needle.
The Pharmaceutical form and dosage is a suspension for injection in pre-filled syringe (the vaccine appears as a milky-white suspension).
The Pharmacotherapeutic group is Influenza vaccine, ATC code: J07BB02

II.2 Drug Substance

The Drug Substance is a sterile suspension containing predominantly the purified outer membrane proteins, haemagglutinin (HA) and neuraminidase (NA), of one of the influenza virus strains selected annually by the WHO/CHMP/CBER/CDC. Traces of viral envelope parts may be present. The Drug Substance (Monovalent Pooled Harvest) from each of the three selected viral strains will be combined to produce the trivalent bulk product.
The chemical-pharmaceutical documentation and Quality Overall Summary in relation to INNOFLU are not of sufficient quality in view of the present European regulatory requirements. Stability studies have been performed with the drug substance.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained.
The stability reports provided for the pre-filled syringes refer to the product Fluad, however, as aTIV has the same composition, the stability data can be accepted.
As regards season 2015-2016, results up to 9 months only are provided; the applicant should provide the final report.
Data supporting the stability of Fluad influenza vaccine filled in syringes luer cone with tip cap new formulation are acceptable.
The Company should commit to report stability data if outside specification.

II.4 Discussion on chemical, pharmaceutical and biological aspects

III. NON-CLINICAL ASPECTS

III.1 Introduction

The nonclinical support for Fluad is based on pharmacology and toxicology studies in several species. Primary pharmacology studies were performed in mice. Mice are appropriate for the study of influenza because they respond immunologically to vaccination, and can be infected with the influenza virus. These studies, performed via the subcutaneous or intramuscular routes, demonstrated that immunization of both young and old mice with influenza vaccines, either alone or in combination with MF59, elicits a dose-related antigen-specific antibody response, even in seropositive mice.
Excipients or chemical substances used in the manufacturing process or in the final product do not raise a concern in relation to potential carcinogenicity. Extremely low levels of exposure to any contaminant or impurity would result from annual dosing of Fluad.
Other potential safety concerns with respect to the use of Fluad in humans include hypersensitivity reactions to vaccine ingredients or residuals from the manufacturing process, and interactions with ongoing therapy that could diminish antibody response to active immunization. These concerns will be addressed by means of appropriate labeling.
In conclusion, the immunogenicity, protection, toxicity, and tolerability of Fluad have been demonstrated in the nonclinical program, and the nonclinical results have been confirmed in clinical testing and marketing experience.

III.2 Pharmacology

Immunogenicity and challenge experiments with Fluad were performed in mice and rabbits. The mouse is an appropriate species because, although the mouse is not a natural host for the influenza virus, it can be a good predictor of the human response to influenza infection and vaccination. Rabbits are commonly used to assess the local and systemic toxicity of vaccines, because vaccines

elicit an appropriate pharmacological response (antibodies), and the rabbit is of sufficient size to allow administration of the full clinical dose of vaccine, using the clinical route of administration and multiple blood draws.
Primary pharmacology studies were performed using the subcutaneous or intramuscular routes of administration.
In accordance with guidelines on the nonclinical development of vaccines, no secondary pharmacodynamic, safety pharmacology, or pharmacodynamic drug interaction studies were performed with Fluad. Safety pharmacology was assessed following administration of MF59 in dogs; there were no effects on cardiovascular and neurological parameters.

III.3 Pharmacokinetics

No pharmacokinetics studies of any type were performed with Fluad because these studies are not relevant for vaccines.
Studies performed with MF59 adjuvant to assess distribution and clearance are described. No pharmacokinetic studies were performed to assess drug interactions with MF59, and no other pharmacokinetic studies were performed with MF59, because these studies are normally not needed according to The Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines (CPMP/SWP/465/95).

III.4 Toxicology

The nonclinical support for Fluad is based on pharmacology and toxicology studies in several species. Primary pharmacology studies were performed in mice. Mice are appropriate for the study of influenza because they respond immunologically to vaccination, and can be infected with the influenza virus. These studies, performed via the subcutaneous or intramuscular routes, demonstrated that immunization of both young and old mice with influenza vaccines, either alone or in combination with MF59, elicits a dose-related antigen-specific antibody response, even in seropositive mice. Other beneficial effects associated with immunization included proliferation of spleen-derived lymphocytes, reduction in lung viral load following subsequent challenge with influenza virus, and, more importantly, protection against challenge with lethal doses of influenza virus up to 200 days post-vaccination. In all cases, the presence of the adjuvant significantly increased the immune response, in both young and old mice.
Fluad was also administered to female rabbits by intramuscular injection at the clinical dose and volume twice before mating and twice during gestation. Fluad was immunogenic in maternal rabbits, developing fetuses had comparable titers, and antibodies persisted through the first 4 weeks of life in F1 kits.
Fluad, and vaccine lots that are equivalent to Fluad, were tested in toxicology studies. The species selected for these studies, the rabbit, was chosen because influenza antigens elicit an immunologic response, and the full clinical dose and volume of vaccine can be administered using the clinical route of administration. The toxicology program fulfills current regulatory expectations for the nonclinical testing of vaccines (CPMP/SWP/465/95 and WHO Technical Report No. 927, 2005) and adjuvants (EMEA/CHMP/VEG/134716/2004) with the following exception: all tissues specified in the WHO Technical Report were not evaluated histopathologically in the pivotal Fluad repeat-dose toxicity studies. This is not considered a deficiency because influenza vaccines are well understood toxicologically, as is MF59 adjuvant, and all major organs and tissues of the immune system were evaluated.
A GLP Guinea pig study was conducted to assess potential for delayed contact hypersensitivity using the Magnusson-Kligman Maximization Test. Fluad did not cause hypersensitivity.
Mutagenicity and carcinogenicity studies have not been conducted with Fluad. These studies are not required for vaccine products that are administered infrequently. Regarding MF59, the adjuvant is not genotoxic (Ames test) or clastogenic (mouse micronucleus), is not a dermal sensitizer (Guinea pig), and was not teratogenic (rat and rabbit) or a developmental toxicant (rat).

Excipients or chemical substances used in the manufacturing process or in the final product do not raise a concern in relation to potential carcinogenicity. Extremely low levels of exposure to any contaminant or impurity would result from annual dosing of Fluad.
Other potential safety concerns with respect to the use of Fluad in humans include hypersensitivity reactions to vaccine ingredients or residuals from the manufacturing process, and interactions with ongoing therapy that could diminish antibody response to active immunization. These concerns will be addressed by means of appropriate labeling.
In conclusion, the immunogenicity, protection, toxicity, and tolerability of Fluad have been demonstrated in the nonclinical program, and the nonclinical results have been confirmed in clinical testing and marketing experience.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Inactivated vaccine products are exempted due to the nature of their constituents (EMA/CHMP/VWP/457259/2014)

III.6 Discussion on the non-clinical aspects

The Applicant has provided the updated sections of the Dossier as requested

IV. CLINICAL ASPECTS

IV.1 Introduction

Clinical immunogenicity and safety studies submitted have demonstrated the non-inferiority of aTIV with respect to non-adjuvanted comparators, but also an increase of magnitude of HI antibody responses in elderly vaccine recipients, even if, after adjustment for multiplicity, a superiority with respect to TIV has not been demonstrated for general studied population nor for high risk subpopulation. Moreover, these differences have been observed also for heterologous strains, potentially as a result of expanded epitope recognition, even if a superiority has not been demonstrated after adjustment for multiplicity. Immunogenicity data also show an enhancement of HI antibody persistence.
Although it remains to be established in randomized clinical trials whether the incremental improvements in immunogenicity associated with aTIV will translate to improved clinical efficacy, available experimental evidence suggests that a relationship exists since higher levels of HI antibody are directly related to clinical protection.
Enhancements in immunogenicity in comparison to non-adjuvanted TIV are also evident upon repeated (annual) vaccination, regardless of whether the same or an updated antigen is administered, with no demonstrable changes in safety profile.
Clinical effectiveness studies support the potential for improved clinical efficacy following vaccination with aTIV, as confirmed by the results of the observational study C70P1 (a.k.a. “LIVE”) conducted in Italy and the observational case-control study V70_49OBTP conducted in Canada.
The therapeutic indication applied for is: Active immunization against influenza in the elderly (65 years of age and over), especially for those with an increased risk of associated complications.

IV.2 Pharmacokinetics

No clinical pharmacology studies, including pharmacokinetic studies, were performed in the aTIV development program because kinetic properties of influenza vaccines do not provide relevant information for establishing adequate dosing recommendations. In the absence of specific requirements in the May 2007 CBER Guidance Document, the vaccine dose, schedule, and formulation have been based on those of licensed influenza vaccines; and pertinent data from clinical studies V7P38 and V104P3.

IV.3 Pharmacodynamics

Pharmacotherapeutic group: Influenza vaccine, ATC code: J07BB02
The immune response of aTIV has been evaluated in 16 randomized controlled trials including 16.974 subject vaccinated with aTIV (n=5869) or a non-adjuvanted vaccine (n=5236).
Seroprotection is generally obtained within 2 to 3 weeks. The duration of post vaccination immunity to homologous strains or to strains closely related to the vaccine strains varies, but it is usually 6-12 months.
Although comparative field efficacy trials have not been performed, the antibody response to aTIV is increased when compared to the response to vaccines without adjuvant, and is most pronounced for B and A/H3N2 influenza antigens.
This increased response is seen particularly in elderly subjects with low pre-immunisation titre and/or with underlying diseases (diabetes, cardiovascular and respiratory diseases) who are at increased risk of complications of influenza infection. A similar immunogenicity profile has been noted after a second and third immunisation with aTIV. Significant antibody rises after immunisation with aTIV have also been shown against heterovariant strains, antigenically different from those included in the vaccine.

IV.4 Clinical efficacy - Clinical safety

The immune response of aTIV has been evaluated in 16 randomized controlled trials including 16.974 subject vaccinated with aTIV (n=5869) or a non-adjuvanted vaccine (n=5236).
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This increased response is seen particularly in elderly subjects with low pre-immunisation titre and/or with underlying diseases (diabetes, cardiovascular and respiratory diseases) who are at increased risk of complications of influenza infection. A similar immunogenicity profile has been noted after a second and third immunisation with aTIV.
Significant antibody rises after immunisation with aTIV have also been shown against heterovariant strains, antigenically different from those included in the vaccine.
The clinical effectiveness of aTIV has been evaluated in two observational studies:

Observational studies:
The first study (Study C70P1) was an observational prospective cohort study performed in 5 Northern Italian health districts during the 2006-7, 2007-8 and 2008-9 influenza seasons. The study objective was to assess the relative risk of hospitalizations for influenza or pneumonia during the influenza season amongst subjects 65 years of age or older who received either aTIV or a non-adjuvanted vaccine. The choice of influenza vaccine for each study subject, either aTIV or a non-adjuvanted vaccine, was left to the individual provider to be determined on the basis of local influenza vaccination policy. This multi-year study enrolled 107,661 elderly subjects, 65 years of age or older, with 43,667 subjects participating for more than 1 year. In total, 88,449 doses of aTIV and 82,539 doses of non adjuvanted vaccine were administered. Predefined windows during the influenza season were used to determine the primary endpoint of hospitalization due to influenza or pneumonia, but laboratory based confirmation of influenza was not performed. Due to local immunization policy, subjects who received aTIV often had worse baseline health status than those subjects who received a non- adjuvanted vaccine. After adjusting for confounding variables (baseline health status, others), the risk of hospitalization for influenza or pneumonia was 25% lower for aTIV relative to non-adjuvanted vaccine (relative risk = 0.75, 95% confidence interval: 0.57, 0.98).

The second study (study V70-49OBTP) was a retrospective case-control study evaluating vaccine effectiveness of aTIV, a non-adjuvanted comparator, or no vaccination. Cases and controls were identified from the influenza tests performed in the population served by three main health authorities in British Columbia and analysed at a central provincial laboratory. In total 84 cases and 198 controls of 65 years of age or older were enrolled (165 vaccinated with aTIV, 62 with a non-adjuvanted influenza vaccine and 55 unvaccinated subjects). The majority of the participants reported at least one chronic disease (89%). The most commonly reported chronic disease categories were cardiac (72%) followed by neurological (39%) and respiratory condition (30%). Cases were defined as RT-PCR confirmed influenza following onset of influenza-like illness (ILI). Controls were individuals with similar characteristics, but who tested negative for influenza. After adjusting for confounding variables (age, sex, residency in a long-term care facility, chronic conditions, region and week of testing), the absolute vaccine effectiveness for aTIV was 58% (CI: 5-82, p<0.04) and non-adjuvanted vaccine was ineffective. The relative vaccine effectiveness for aTIV was 63% (CI: 4-86. P=0.04) as compared to non-adjuvanted influenza vaccine.

Randomized controlled interventional studies:

Study V70-27-01 is a Phase 3, randomized, controlled, observer-blind, multicenter study to evaluate the immunogenicity, the safety and the consistency of three consecutive lots of aTIV in comparison to non-adjuvanted vaccine and it was conducted in 2010-2011. Subjects were randomized in a 1:1:1:3 ratio to receive a single 0.5 mL dose of 1 of 3 consecutive lots of aTIV or a single lot of a non-adjuvanted influenza vaccine. All subjects were followed for approximately one year post-vaccination. A total of 7082 subjects were randomized and vaccinated, including 3541 subjects in each of the pooled aTIV and non-adjuvanted vaccine groups. A total of 2573 subjects (1300 in aTIV and 1273 in non-adjuvanted vaccine group) were regarded as “high risk” subjects (underlying chronic diseases including congestive heart failure, chronic obstructive pulmonary disease, asthma, hepatic disease, renal insufficiency and/or neurological/neuromuscular or metabolic disorders including diabetes mellitus).

The primary objective of a superiority of aTIV versus non-adjuvanted vaccine was not achieved for all homologous strains; the co-primary objective of a non-inferiority of aTIV versus non-adjuvanted vaccine was achieved for all homologous strains; however significantly higher HI titers rates against all three homologous strains of influenza at day 22 post vaccination were seen in subjects that received aTIV compared with non-adjuvanted influenza vaccine (Table 1). The results were similar for high risk subjects with predefined comorbidities. Immunogenicity data supported similar antibody responses across aTIV lots; CHMP criteria were met for aTIV.

In addition, in a subset of subjects (n=1649 subjects), aTIV was compared to the non-adjuvanted influenza vaccine for heterologous strains, i.e. influenza variants of the same type/subtype that were not included in the vaccine composition (secondary objective). Superiority of aTIV as compared to non-adjuvanted influenza vaccine was not achieved for all 3 heterologous strains at day 22; however non-inferiority was demonstrated for all 3 heterologous strains at day 22. Results were similar for high risk subjects (609 subjects)

Table 1: Postvaccination GMTs and Vaccine Group Ratios - HI assay

Study	Antigen	aTIV		Non-adjuvanted Vaccine		
		N	GMT (95% CI)	N	GMT (95% CI)	Vaccine Group Ratio (95% CI)
All subjects[a]	H3N2	3225	544 (513-575)	3256	337 (319-357)	1.61 (1.52-1.7)[§]
	H1N1	3225	198 (185-211)	3257	141 (132-150)	1.4 (1.32-1.49)[§]
	B	3227	55 (52-58)	3259	48 (46-51)	1.15 (1.08-1.21)[§]
High risk subjects[a]	H3N2	1194	519 (477-565)	1190	331 (304-360)	1.57 (1.44-1.72)[§]
	H1N1	1194	221 (201-243)	1190	161 (146-177)	1.38 (1.25-1.52)[§]
	B	1195	61 (56-66)	1190	54 (50-59)	1.12 (1.03-1.21)[§]

HI: Hemagglutination inhibition assay; GMT: Geometric Mean HI titers; CI: Confidence Interval
[a]Postvaccination (Day 22) GMTs and vaccine group GMT ratios (aTIV: non-adjuvanted influenza vaccine) are adjusted for baseline titer, country and age cohort; Per Protocol Population.
[§] As the lower limit of the 95% CI of the vaccine group ratio is greater than 1, it regarded that HI titers after vaccination with aTIV are higher than those of the nonadjuvanted influenza vaccine.

A specific analysis for safety in the "high risk" population was not performed; for the complete population an higher percentage of subjects in the aTIV group than in the non-adjuvanted vaccine reported local reaction (32% vs 17%) and systemic reactions (32% vs 26%). The overall safety profile showed similar incidences of unsolicited AEs and SAEs for aTIV and non-adjuvanted influenza vaccine.
The second study (M63P1) is a phase 3, randomized, active-controlled, observer-blind, multicenter study to evaluate immunogenicity and safety of aTIV in subjects 65 years of age and older with underlying chronic medical conditions. 350 frail elderly subjects were enrolled and randomized 1:1 to receive aTIV (n=175) or non-adjuvanted influenza vaccine (n=175), all of whom had underlying chronic medical conditions including congestive heart failure, chronic obstructive pulmonary disease (COPD) or asthma, hepatic or renal insufficiency, arteriosclerotic disease or diabetes mellitus and rheumatoid arthritis.
The GMT against A/H3N2 influenza strain 21 days after administration of aTIV did not meet the superiority criteria when compared to a non-adjuvanted inactivated split influenza virus vaccine (primary objective). Seroconversion was obtained for 85% (A/H3N2), 87% (A/H1N1) and 88% (B) of subjects. CHMP criteria for efficacy were met for aTIV.
A small increase in primarily mild local reactogenicity and a slightly higher percentage of systemic reactions were noted for aTIV compared to non-adjuvanted influenza vaccine. The overall safety profile showed similar incidences of unsolicited AEs and SAEs for aTIV and non-adjuvanted influenza vaccine.

IV.5 Risk Management Plan

The MAH has submitted the Risk Management Paln version 4.0 as requested 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 INNOFLU.
This version of RMP was already evaluated (Type IB variation IT/H/102/01/1B/114) with positive outcome the 09/05/2017.

V. USER CONSULTATION

The MAH declares that the consultation with target groups has not been performed because the labelling of the adjuvanted trivalent influenza vaccine (Innoflu in Italy and Fluad in UK) included in the new marketing authorization application with procedure IT/H/0525/01/DC are the same as the ones already authorized for the same product FLUAD registered via MRP (IT/H/0104/01) which already complies with EU regulation and no significant change has been introduced.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The balance of benefits and risks supports the use of aTIV for active immunization of adults 65 years of age and older against influenza disease caused by influenza virus subtypes A and B contained in the vaccine.
However in all clinical sections of the dossier, the Applicant states that the marketing authorization is requested for the aTIV vaccine intended for the US market, that is equivalent to the formulation marketed in other countries since 2000.
Furthermore the Applicant states that non-inferiority and superiority studies have been conducted using as comparator Agriflu (trivalent non adjuvated vaccine) authorized in US and equivalent to Agrippal, that was approved in the US on 2009 for individuals 18 years of age and older.
All above considered, the marketing authorization request is approvable.