SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fluad, suspension for injection in pre-filled syringe

Influenza Vaccine, Surface Antigen, Inactivated, Adjuvanted with MF59C.1

(2016/2017 SEASON)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Influenza virus surface antigens (haemagglutinin and neuraminidase), of strains*:

A/California/7/2009 (H1N1) pdm09 – like strain (A/California/7/2009, NYMC X-181)

15 micrograms HA**

A/Hong Kong/4801/2014 (H3N2) – like strain (A/Hong Kong/4801/2014, NYMC X-263B)

15 micrograms HA**

B/Brisbane/60/2008 – like strain (B/Brisbane/60/2008, wild type)

15 micrograms HA**

*propagated in fertilized hens' eggs from healthy chicken flocks and adjuvanted with MF59C.1

**haemagglutinin

Adjuvant: MF59C.1 which is an exclusive adjuvant: 9.75 mg squalene, 1.175 mg polysorbate 80, 1.175 mg sorbitan trioleate, 0.66 mg sodium citrate, 0.04 mg citric acid, water for injections.

For one dose of 0.5 ml

This vaccine complies with the WHO recommendations (Northern Hemisphere) and EU decision for the 2016/2017 season.

Fluad may contain traces of eggs such as ovalbumin or chicken proteins, kanamycin and neomycin sulphate, formaldehyde, cetyltrimethylammonium bromide (CTAB) and barium sulphate which are used during the manufacturing process (see section 4.3).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection in pre-filled syringe.

The vaccine appears as a milky-white suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Active immunisation against influenza in the elderly (65 years of age and over), especially for those with an increased risk of associated complications.

The use of Fluad should be based on official recommendations.

4.2 Posology and method of administration

Posology

A single 0.5 ml dose 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.

Method of administration

For instructions for preparation, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances, components of the adjuvant, excipients, residues (e.g., egg or chicken proteins, such as ovalbumin) or in anyone who has had an anaphylactoid reaction to previous influenza vaccination.

The vaccine may contain residues of the following substances: kanamycin and neomycin sulphate, formaldehyde, cetyltrimethylammonium bromide (CTAB) and barium sulphate.

Immunisation shall be postponed in patients with febrile illness or acute infection.

4.4 Special warnings and precautions for use

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

Fluad should under no circumstances be administered intravascularly or subcutaneously.

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions, can occur following, or even before, any vaccination as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

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

A protective response may not be elicited in all vaccinees.

Latex-sensitive individuals:
Although no natural rubber latex is detected in the syringe tip cap, the safe use of Fluad in latex-sensitive individuals has not been established.

4.5 Interaction with other medicinal products and other forms of interaction

No clinical data on concomitant administration with other vaccines are available.

If Fluad needs to be used at the same time as another vaccine, immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

A higher frequency of some solicited systemic reactions has been reported in subjects vaccinated with trivalent inactivated influenza vaccine and pneumococcal vaccine compared with trivalent inactivated influenza vaccine alone.

The immunological response may be diminished 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 observed. The Western Blot technique disproves the false-positive ELISA results. The transient false positive reactions could be due to the IgM response by the vaccine.

4.6 Fertility, pregnancy and lactation

Not applicable.

4.7 Effects on ability to drive and use machines

Fluad has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

A higher incidence of mild post-immunisation reactions has been reported with Fluad compared to non-adjuvanted influenza vaccines.

Adverse reactions observed from clinical trials

The safety of the adjuvanted trivalent influenza vaccine (aTIV) in elderly subjects was assessed in thirty-six (36) clinical trials in subjects ≥65 years of age, including 19 randomized controlled trials and 17 uncontrolled seasonal studies. This database includes 12730 subjects, 7532 subjects who received aTIV and 5198 subjects who received conventional trivalent influenza vaccines (TIV).

In this pooled analysis, a higher percentage of subjects who received aTIV reported both local and systemic reactions post-immunization compared with those that received conventional TIV. These included pain at injection site (26.1 vs 13.7%), local tenderness (22.2 vs 12.2%), erythema (3.2 vs 1.7%), induration (2.5 vs 1. 2 %) and swelling (1.6 vs 0.6%) in addition to myalgia (11.0 vs 7.9%) chills (5.0 vs 4.0%), fatigue (11.3% vs 10.5%) and malaise (6.3% vs 5.8%).

The following undesirable effects have been observed during clinical trials with the following frequencies:

Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports.

Nervous system disorders

Very common (≥1/10): Headache

Gastrointestinal disorders

Common (≥1/100, <1/10): Nausea, Diarrhoea, Vomiting

Skin and subcutaneous tissue disorders

Common (≥1/100, <1/10): Sweating

Uncommon (≥1/1,000, <1/100): Rash

Musculoskeletal and connective tissue disorders

Very common (≥1/10): Myalgia

Common (≥1/100, <1/10): Arthralgia

General disorders and administration site conditions

Very common (≥1/10): Tenderness, pain at injection site, fatigue

Common (≥1/100, <1/10): Fever, malaise, shivering

Local reactions: redness, swelling, ecchymosis, induration

Most reactions are mild or moderate and resolve spontaneously within 1 to 2 days.

Adverse reactions reported from post-marketing surveillance

Adverse reactions reported from post marketing surveillance are, next to the reactions which have also been observed during the clinical trials, the following:

Blood and lymphatic system disorders

Thrombocytopenia (some very rare cases were severe with platelet counts less than 5,000 per mm^3), lymphadenopathy.

General disorders and administration site conditions

Asthenia, Influenza-Like Illness (ILI).

Extensive swelling of injected limb lasting more than one week, injection-site cellulitis-like reaction (some cases of swelling, pain and redness extending more than 10 cm and lasting more than one week).

Immune system disorders

Allergic reactions including anaphylactic shock (in rare cases), anaphylaxis and angioedema.

Musculoskeletal and connective tissue disorders

Pain in the extremity, muscular weakness.

Nervous system disorders

Encephalomyelitis, Guillain-Barré Syndrome, convulsions, neuritis, neuralgia, paraesthesia, syncope, presyncope.

Skin and subcutaneous tissue disorders

Generalised skin reactions including erythema multiforme, urticaria, pruritus or non-specific rash.

Vascular disorders

Vasculitis with transient renal involvement.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Overdosage is unlikely to have any untoward effect.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

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.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated-dose toxicity, local tolerance and sensitisation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Adjuvant: see section 2.

Other: sodium chloride, potassium chloride, potassium dihydrogen phosphate, disodium phosphate dihydrate, magnesium chloride hexahydrate, calcium chloride dihydrate and water for injections.

6.2 Incompatibilities

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

6.3 Shelf life

1 year

6.4 Special precautions for storage

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

6.5 Nature and contents of container

0.5 ml of suspension for injection in pre-filled syringe (type I glass), presented with or without needle.

Pack of 1x, with or without needle.

Pack of 10x, with or without needle.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

After shaking, the normal appearance of Fluad is a milky-white suspension.

Visually inspect the contents of each Fluad pre-filled syringe for particulate matter or discoloration prior to administration. If either condition is observed, do not use the contents.

Do not use if the vaccine has been frozen.

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

7 MARKETING AUTHORISATION HOLDER

Seqirus S.r.l., Via Fiorentina 1, 53100 Siena, Italy

8 MARKETING AUTHORISATION NUMBER(S)

PL 46752/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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