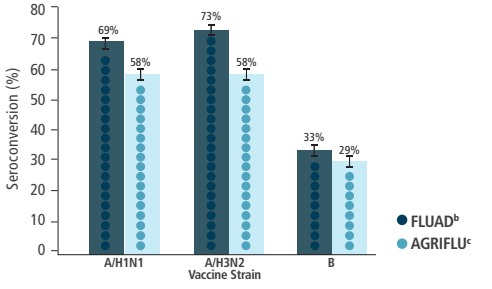
This article was sponsored by Seqirus Inc.

FLUAD™ (influenza vaccine, adjuvanted) to Help Protect Elderly Patients Against Influenza

Influenza affects elderly patients disproportionately, with an estimated 50% to 70% of hospitalizations and 80% to 90% of deaths from influenza occurring in adults 65 years or older.[1] Among patients with underlying chronic comorbid conditions, such as acute ischemic heart disease, stroke, or pneumonia, influenza is the most common cause of mortality during the winter months.[2] Symptoms of influenza in older adults may include anorexia, malaise, weakness, dizziness, profuse sweating, and mottled extremities.[3] Annual vaccination, which is recommended by the CDC for everyone 6 months or older, can help reduce severe outcomes in patients at risk, such as those 65 years or older.[1,4]

Figure 1: Noninferiority Established Based on Seroconversion Rates at Day 22[10,a]



Differences in seroconversion rate[d] (95% CI)	A/H1N1	A/H3N2	B
	9.8% (7.5%-12.1%)	13.9% (11.7%-16.1%)	3.2% (1.1%-5.3%)

[a]Results obtained following vaccination with influenza vaccine formulated for the 2010-2011 season.
[b]N = 3225-3227, the number of vaccinated participants with available data for the immunologic end point listed.
[c]N = 3256-3259, the number of vaccinated participants with available data for the immunologic end point listed.
[d]FLUAD met noninferiority criteria based on seroconversion rate differences if the lower limit of the 95% CI [FLUAD-AGRIFLU] for each strain was ≥10%.

Unique Challenges in Elderly Patients

The elderly population is unique because of age-related declines in immune function. These complex changes, known as immunosenescence, can result in poorer response to influenza vaccination in adults older than 65 years.[5,6] Both the initial and long-term immune responses to vaccinations are compromised in these patients.[6]

Scientists have developed strategies for improving vaccine-mediated protection against influenza in the elderly population. One product is the high-dose influenza vaccine, which contains 4 times as much antigen as the standard influenza vaccine. Other products have attempted to augment local immunity by administering the influenza vaccine intradermally.[7] FLUAD™ (influenza vaccine, adjuvanted) contains the proprietary adjuvant MF59®, which has demonstrated a strong immune response in a standard dose and which is hypothesized to increase immune cell recruitment at the injection site and augment the process of antigen presentation.[8]

Until the 1997 approval of FLUAD in Italy, early 20th century aluminum-based products were the only available adjuvanted vaccines on the market.[8,9] Since then, the immunogenicity of the MF59-adjuvanted influenza vaccine has been confirmed in a pivotal trial (N = 3225-3227 in the FLUAD group) in adults 65 years or older. To date, more than 81 million doses of FLUAD have been distributed in more than 30 countries where it is approved.[8,10,11]

Clinical Study of Immunogenicity of FLUAD

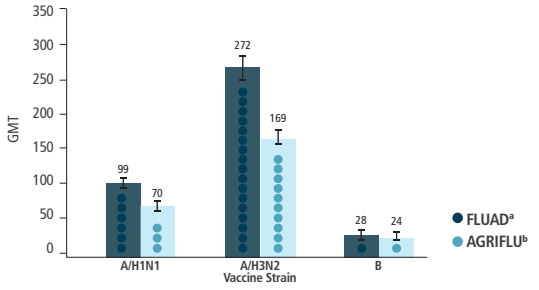
In the pivotal clinical trial for FLUAD, adults 65 years or older, with a mean age of 72 years, received FLUAD (N = 3545) or AGRIFLU (influenza vaccine) (N = 3537), a US-licensed non-adjuvanted influenza vaccine. Clinical immunogenicity was assessed in 91% of subjects receiving FLUAD and 92% of subjects receiving AGRIFLU at day 22 after the vaccination. In an analysis designed to assess noninferiority, researchers assessed seroconversion rates and geometric mean antibody titer ratios. Noninferiority was established for both outcome measures (Figures 1 and 2).[10]

Safety Considerations for FLUAD

Key safety considerations with FLUAD include its contraindication for use in patients who have previously experienced an allergic reaction to any vaccine component, including egg protein. Consideration of the benefits and risks of administering the influenza vaccine should be made in any patient who experienced Guillain-Barré Syndrome within 6 weeks of receiving a previous influenza vaccine. Because the tip cap of the prefilled FLUAD syringe con-

Please see Brief Summary of full Prescribing Information on following pages.

Figure 2: Noninferiority Established Based on GMTs and GMT Ratios at Day 22[10]



	A/H1N1	A/H3N2	B
GMT ratio[c] (95% CI)	1.4 (1.32-1.49)	1.61 (1.52-1.7)	1.15 (1.08-1.21)

GMT = geometric mean antibody titer.
[a]N = 3225-3227; this is the number of vaccinated participants with available data for the immunologic end point listed.
[b]N = 3256-3259; this is the number of vaccinated participants with available data for the immunologic end point listed.
[c]FLUAD met noninferiority criteria based on GMT ratios if the lower limit of the 95% CI [FLUAD: AGRIFLU] for each strain was >0.67.

tains natural rubber latex, allergic reactions may occur in individuals with latex sensitivity who receive the vaccine. The most common local adverse reactions in the pivotal clinical trial included injection site pain (25%) and tenderness (21%), whereas systemic adverse reactions included myalgia (15%), headache (13%), and fatigue (13%). These adverse events (AEs) were solicited, and while higher rates of solicited AEs were noted with FLUAD, they were typically mild to moderate in severity.[10]

Role of the Pharmacist

Data show that a growing number of elderly patients receive their annual influenza vaccine from their pharmacist. Influenza vaccinations are available in pharmacies in all 50 states, which has resulted in improved influenza vaccination rates in the elderly population.[12,13]

Patients can look to their pharmacist to provide a vaccine with characteristics that will best serve them. By providing education about the important characteristics of FLUAD, pharmacists can potentially provide their patients 65 years or older with an influenza vaccine specifically designed for their needs to help protect them against influenza.

Important Safety Information

INDICATIONS

FLUAD is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. FLUAD is approved for use in persons 65 years of age and older.

CONTRAINDICATIONS

Severe allergic reaction to any component of the vaccine, including egg protein, or after a previous dose of any influenza vaccine.

WARNINGS AND PRECAUTIONS

- If Guillain-Barré Syndrome (GBS) has occurred within six weeks of previous influenza vaccination, the decision to give FLUAD should be based on careful consideration of the potential benefits and risks.
- The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

ADVERSE REACTIONS

- The most common (≥10%) local (injection site) adverse reactions observed in clinical studies were injection site pain (25%) and tenderness (21%).
- The most common (≥10%) systemic adverse reactions observed in clinical studies were myalgia (15%), headache (13%) and fatigue (13%).

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Please see Brief Summary of full Prescribing Information on following pages.

GMCC-804_2016-03-23

FLUAD (Influenza Vaccine, Adjuvanted)

Suspension for Intramuscular Injection
2015-2016 Formula
Initial U.S. Approval: 2015

BRIEF SUMMARY:

See package insert for full prescribing information.

1 INDICATIONS AND USAGE

FLUAD is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. FLUAD is approved for use in persons 65 years of age and older. Approval is based on the immune response elicited by FLUAD. Data demonstrating a decrease in influenza disease after vaccination with FLUAD are not available. [see Clinical Studies (14)]

4 CONTRAINDICATIONS

Do not administer FLUAD to anyone with a history of severe allergic reaction (e.g. anaphylaxis) to any component of the vaccine, including egg protein [see Description (11)], or to a previous influenza vaccine.

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

If Guillain-Barré syndrome (GBS) has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give FLUAD should be based on careful consideration of the potential benefits and risks. The 1976 swine influenza vaccine was associated with an elevated risk of GBS. Evidence for a causal relationship of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than 1 additional case per 1 million persons vaccinated. *[see References (1)]*

5.2 Preventing and Managing Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

5.3 Latex

The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions in latex sensitive individuals. *[see Description (11)]*

5.4 Altered Immunocompetence

The immune response to FLUAD in immunocompromised persons, including individuals receiving immunosuppressive therapy, may be lower than in immunocompetent individuals. *[see Concurrent Use With Immunosuppressive Therapies (7.2)]*

5.5 Syncope

Syncope (fainting) may occur in association with administration of injectable vaccines including FLUAD. Ensure procedures are in place to avoid injury from falling associated with syncope.

5.6 Limitations of Vaccine Effectiveness

Vaccination with FLUAD may not protect all vaccine recipients against influenza disease.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect rates observed in clinical practice.

Solicited adverse reactions were assessed in a multicenter, observer-blind, randomized controlled study (Study 1) conducted in the United States, Colombia, Panama and the Philippines. The safety analysis set included 3545 FLUAD recipients and 3537 AGRIFLU (Influenza Vaccine) recipients. The enrolled subject population in Study 1 was 65 to 97 years of age (mean 72 years) and 64% were female. Within each treatment group, 53% were Asian, 28% were Caucasian, 18% were Hispanic, 1% were Black, and fewer than 1% each were Native American/ Alaskan, Pacific Islander/Hawaiian, or Other.

Solicited local (injection site) and systemic adverse reactions were collected from subjects in Study 1 who completed a symptom diary card for seven days following vaccination. The reported frequencies of solicited local and systemic adverse events from Study 1 are presented in Table 1.

Table 1. Percentages of Subjects ≥ 65 Years of Age With Solicited Local and Systemic Adverse Reactions in Days 1-7 After Administration of FLUAD or AGRIFLU (a U.S. Licensed Comparator) NCT01162122

Study 1			
		FLUAD (N[a]=3418-3496) Percentage	AGRIFLU (N[a]=3420-3488) Percentage
Local			
Injection site Pain	Any	25.0	12.2
	Moderate[b]	3.9	1.9
	Severe[c]	0.3	0.2
Tenderness	Any	21.1	11.2
	Moderate	3.0	1.0
	Severe	0.1	0.2
Erythema	Any	1.2	0.5
	25 to ≤ 50 mm	1.1	0.5
	51 to ≤ 100 mm	0.2	<0.1
	> 100 mm	0.0	0.0
Induration	Any	1.3	0.5
	25 to ≤ 50 mm	1.0	0.5
	51 to ≤ 100 mm	0.3	0.0
	> 100 mm	0.0	0.0
Swelling	Any	1.2	0.4
	25 to ≤ 50 mm	1.0	0.4
	51 to ≤ 100 mm	0.2	<0.1
	> 100 mm	<0.1	0.0

Systemic			
Myalgia	Any	14.7	9.7
	Moderate	2.6	1.8
	Severe	0.3	0.7
Fatigue	Any	13.3	10.4
	Moderate	3.1	2.4
	Severe	0.4	0.6
	PLT[d]	0.0	<0.1
Headache	Any	13.2	11.2
	Moderate	3.0	2.6
	Severe	0.4	0.6
	PLT	0.0	<0.1
Arthralgia	Any	8.5	7.8
	Moderate	1.6	1.6
	Severe	0.2	0.6
Chills	Any	6.7	4.7
	Moderate	1.5	1.2
	Severe	0.3	0.3
	PLT	<0.1	0.0
Diarrhea	Any	4.8	4.5
	Moderate	1.3	0.9
	Severe	0.3	0.2
	PLT	<0.1	<0.1
Fever	Any	3.6	3.4
	≥ 38.0°C to ≤ 38.4°C	1.8	1.7
	≥ 38.5°C to ≤ 38.9°C	1.3	1.3
	39.0°C to ≤ 40.0°C	0.4	0.4
	≥ 40.0°C	0.1	0.0
Nausea	Any	2.9	2.8
	Moderate	0.4	0.6
	Severe	0.1	0.1
	PLT	<0.1	0.0
Vomiting	Any	1.4	1.7
	Moderate	0.4	0.5
	Severe	<0.1	0.1
	PLT	<0.1	0.0

[a] N = number of subjects with safety data.

[b] Moderate: pain, tenderness, myalgia, fatigue, headache, arthralgia, chills, nausea, vomiting defined as "some limitation in normal daily activity", diarrhea defined as "4 to 5 stools a day".

[c] Severe: pain, tenderness, myalgia, fatigue, headache, arthralgia, chills, nausea, vomiting defined as "unable to perform normal daily activity", diarrhea defined as "6 or more watery stools a day".

[d] Potentially life threatening (PLT) reaction defined as requiring emergency room visit or hospitalization.

Unsolicited Adverse Events (AEs): The clinical safety of FLUAD was assessed in fifteen (15) randomized, controlled studies. The total safety population in these trials included 10,952 adults 65 years of age and older, comprising 5,754 who received FLUAD and 5,198 who received other US licensed influenza vaccines. The percentage of subjects with an unsolicited AE within 30 days following vaccination was similar between vaccine groups (16.9% FLUAD vs. 18.0% active comparator).

Serious Adverse Events (SAEs) and Deaths: In Study 1, in which subjects were followed for SAEs and deaths for one year following vaccination (N=3,545 FLUAD, N=3,537 AGRIFLU), the percentages of subjects with an SAE were similar between vaccine groups (7% FLUAD vs. 7% AGRIFLU). Four SAEs (1 FLUAD and 3 AGRIFLU) were assessed as related to study vaccination over one year of observation and 2 of these occurred (1 FLUAD and 1 AGRIFLU) within 21 days following study vaccination. There were 98 deaths (n=52 FLUAD, n=46 AGRIFLU) over one year of which none occurred within the first 21 days following vaccination.

In 14 additional randomized, controlled studies, SAEs were collected over a 3 to 4-week period in 4 studies, over a 8-week period in 1 study, and over a 6-month period in 9 studies (N= 2,209 FLUAD, N=1,661 US licensed influenza vaccines). The percentages of subjects with an SAE within 30 days (1.1% FLUAD vs. 1.8% AGRIFLU) or within 6 months (4.3% FLUAD vs. 5.9% AGRIFLU) were similar between vaccine groups. The percentages of deaths within 30 days (0.3% FLUAD vs. 0.6% active comparator) or within 6 months (1.0% FLUAD vs. 1.5% active comparator) were also similar.

Adverse Events of Special Interest (AESIs): Rates of new onset neuroinflammatory and immune mediated diseases were assessed in a post hoc analysis of the 15 randomized controlled studies over the time periods specified above for SAEs. The percentage of subjects with an AESI at any time after vaccination was similar between vaccine groups (0.9% FLUAD vs. 0.9% active comparator). There were no notable imbalances for specific AESIs.

Safety of Annual Revaccination: In 5 of the randomized, controlled trials, subjects were followed for SAEs and deaths for 6 months following revaccination (N=492 FLUAD, N=330 US licensed and non-US licensed influenza vaccines). After the second annual vaccination, the percentages of subjects with an SAE were similar between vaccine groups (6.1% FLUAD vs. 5.5% comparator influenza vaccines); 23 deaths (n=17 FLUAD, n=6 comparator influenza vaccines) were reported. Causes of death included cardiovascular events, malignancy, trauma, gastrointestinal disorders, and respiratory failure. Clinical characteristics of the deaths, including the variable causes, timing since vaccination, and underlying medical conditions, do not provide evidence for a causal relationship with FLUAD.

6.2 Postmarketing Experience

The following adverse events have been spontaneously reported during post-approval use of FLUAD in Europe and other regions since 1997.

Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

Blood and lymphatic system disorders:
Thrombocytopenia (some cases were severe with platelet counts less than 5,000 per mm^3), lymphadenopathy

General disorders and administration site conditions:
Extensive swelling of injected limb lasting more than one week, injection site cellulitis-like reactions (some cases of swelling, pain, and redness extending more than 10 cm and lasting more than 1 week)

Immune system disorders:
Allergic reactions including anaphylactic shock, anaphylaxis and angioedema

Musculoskeletal and connective tissue disorders:
Muscular weakness

Nervous system disorders:
Encephalomyelitis, Guillain-Barré Syndrome, convulsions, neuritis, neuralgia, paraesthesia, syncope, presyncope

Skin and subcutaneous tissue disorders:
Generalized skin reactions including erythema multiforme, urticaria pruritus or non-specific rash

Vascular disorders:
Vasculitis with transient renal involvement

7 DRUG INTERACTIONS

7.1 Concomitant Use With Other Vaccines

There are no data to assess the concomitant administration of FLUAD with other vaccines. If FLUAD is to be given at the same time as other injectable vaccine(s), the vaccine(s) should be administered at different injection sites.

Do not mix FLUAD with any other vaccine in the same syringe.

7.2 Concurrent Use With Immunosuppressive Therapies

Immunosuppressive or corticosteroid therapies may reduce the immune response to FLUAD.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B: A reproductive and developmental toxicity study has been performed in rabbits with a dose level that was approximately 15 times the human dose based on body weight. The study revealed no evidence of impaired female fertility or harm to the fetus due to FLUAD. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this vaccine should be used during pregnancy only if clearly needed.

In a reproductive and developmental toxicity study, the effect of FLUAD on embryo-fetal and post-natal development was evaluated in pregnant rabbits. Animals were administered FLUAD by intramuscular injection twice prior to gestation, during the period of organogenesis (gestation day 7) and later in pregnancy (gestation day 20), 0.5 mL (45 mcg)/rabbit/occasion (approximately 15-fold excess relative to the adult human dose based on body weight). No adverse effects on mating, female fertility, pregnancy, embryo-fetal development, or post-natal development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis.

8.4 Pediatric Use

The safety and effectiveness of FLUAD in the pediatric population has not been established.

8.5 Geriatric Use

Safety and immunogenicity of FLUAD have been evaluated in adults 65 years of age and older. [See *Adverse Reactions (6.1)* and *Clinical Studies (14)*]

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