PRODUCT MONOGRAPH

FLUAD*

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

ATC: J07BB02

Sterile Suspension for Injection

Active Immunizing Agent for the Prevention of Influenza

2013/2014 Strains: an A/California/7/2009 (H1N1)pdm09-like virus
an A(H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011
a B/Massachusetts/2/2012-like virus

Sponsor:

Novartis Vaccines and Diagnostics, Inc.
350 Massachusetts Avenue
Cambridge, MA 02139

Date of Preparation:
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Distributed by:

Novartis Pharmaceuticals Canada Inc.
385 Bouchard Blvd.
Dorval QC H9S 1A9
www.novartis.ca

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular injection	Parenteral / Each 0.5 mL prefilled syringe contains 15 μg of influenza virus haemagglutinin surface antigens from each of the three virus strains, types A and B (see DESCRIPTION)	Polysorbate 80 *For a complete listing see Dosage Forms, Composition and Packaging Section.*

DESCRIPTION

FLUAD* is a trivalent, surface antigen, inactivated influenza virus vaccine adjuvanted with MF59C.1.

The influenza virus strains are individually grown in the allantoic cavity of embryonated hens' eggs inoculated with a specific type of influenza virus suspension containing kanamycin and neomycin sulphate. Each of the influenza virus strains is harvested and clarified separately by centrifugation and filtration prior to inactivation with formaldehyde. The inactivated virus is concentrated and purified by zonal centrifugation. The surface antigens, hemagglutinin and neuraminidase, are obtained from the influenza virus particle by further centrifugation in the presence of cetyltrimethylammonium bromide (CTAB), a process which removes most of the internal proteins. The CTAB is removed from the surface antigen preparation.

The MF59C.1 adjuvant contained in FLUAD* is an oil-in-water emulsion composed of squalene as the oil phase, stabilised with the surfactants polysorbate 80 and sorbitan trioleate, in citrate buffer.

FLUAD* is presented as a sterile, milky-white suspension for intramuscular injection in a prefilled syringe. It has been formulated to contain a total of at least 45 mcg hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 mcg HA of each of the following three influenza strains recommended for the 2013/2014 influenza season: A/California/7/2009 (H1N1)pdm09-like virus; A(H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011 ; and B/Massachusetts/2/2012-like virus, as recommended annually for immunization by the World Health Organisation (WHO) and the National Advisory Committee on Immunization (NACI).

INDICATIONS AND CLINICAL USE

FLUAD* is an inactivated influenza virus vaccine indicated for active immunization against influenza in the elderly (65 years of age and older) (see Part II CLINICAL TRIALS).

Consistently numerically higher immune responses to tested heterovariant and homologous strains were observed for FLUAD* in the elderly population and the difference was statistically significant for some strains and/or some endpoints, as compared to the comparator.

The National Advisory Committee on Immunization (NACI) encourages annual vaccination for all Canadians who have no contraindication (CCDR 2009).

Vaccine should be offered to the elderly up to and even after influenza virus activity is documented in a community.

CONTRAINDICATIONS

FLUAD* is contraindicated in persons with a known hypersensitivity to the active substances, to any of the excipients and to eggs, chicken proteins, kanamycin and neomycin sulphate, formaldehyde, and cetyltrimethylammonium bromide (CTAB), or to anyone who has had a life-threatening reaction to previous influenza vaccination.

For a complete listing of ingredients in the formulation and components of the container, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

General

FLUAD* should under no circumstances be administered by any other route than intramuscularly.

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

Prior to administration of any dose of FLUAD*, the vaccine recipient should be asked about their personal history, family history, and recent health status, including immunization history, current health status, main allergies and any adverse event associated with previous immunizations.

Before the injection of any biological product, such as vaccines, the person responsible for administration should take all precautions known for the prevention of allergic or any other reactions. As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event occurs following administration of the vaccine.

Immunization with FLUAD* should be postponed in patients with febrile illness or acute infections.

Hematologic

As with other intramuscular injections, administration of FLUAD* requires careful consideration in patients with clinically significant bleeding disorders.

Immune

The immune response to FLUAD* in immunocompromised persons, including individuals receiving immunosuppressive therapy, may be lower than in immunocompetent individuals. Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.

Neurologic

If Guillain-Barré syndrome 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.

Monitoring and Laboratory Tests

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 results. The transient false positive reactions could be due to the IgM response by the vaccine.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse event information is derived from both controlled and uncontrolled clinical trials and worldwide post-marketing experience.

Vaccination with FLUAD* cannot cause influenza because the vaccine does not contain live virus. Respiratory disease after vaccination represents coincidental illness unrelated to influenza vaccination.

Allergic-type responses, such as urticarial rash, allergic bronchospasm, or systemic anaphylaxis occur extremely rarely.

The most common FLUAD* local adverse drug reactions are pain at the injection site, temperature at the injection site, and erythema. The incidence of subjects reporting any solicited systemic reactions was generally slightly higher in the FLUAD* than in the comparator group (17% vs. 12%). Reactions are generally mild or moderate and of limited duration. Prophylactic acetaminophen may decrease the frequency of some side effects in adults.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety profile of FLUAD* in adults 65 years and older is based on data from 39 studies. Overall 12,889 subjects were exposed to at least one dose with FLUAD*. Of these 492 received a second consecutive vaccination one year later, and 150 a third FLUAD* vaccine dose the following year. In one study, two doses of FLUAD* were administered 4 weeks apart. In 38 studies solicited local (injection site) and systemic reactions were collected from subjects who completed a symptom diary card for at least four days following vaccination.

Adults 65 Years of Age and Older

Safety data after first vaccination for subjects 65 years of age and older were pooled from 31 trials, safety data after second consecutive vaccination were pooled from five studies and after third consecutive vaccination from two studies.

Pooled Reactogenicity data are provided in Table 1, Table 2 and Table 3.

The most frequently reported solicited local adverse events within 4 days of vaccination were injection site pain, followed by temperature at the injection site ("warm" or "hot") and erythema. Local injection-site reactions (pain and temperature on injection) were more frequent in subjects who received the MF-59 adjuvanted vaccine than in those who received nonadjuvanted vaccine. The frequency of pain was 26% in the FLUAD* group vs. 14% in the comparator group. Temperature at the injection site was 18% in the FLUAD* group vs 11% in the comparator group. Solicited local reactions were generally of mild or moderate intensity, and generally resolved within 2-3 days with 3% or less of subjects reporting a severe local reaction.

The most frequently reported solicited systemic adverse events were headache, fatigue, malaise and myalgia. Most reports of systemic reactions were mild to moderate in severity and generally transient, with 1% or less of subjects reporting a severe systemic reaction across all studies.

In the subset of subjects who received second and third consecutive vaccinations, for both the FLUAD* and the comparator vaccines groups, there was a trend for an increase in the percentage of subjects reporting each local reaction during the 3 days after the second vaccination, compared to the first vaccination, but no further increase after the third vaccination. Overall, systemic reactions were reported by similar percentages of subjects after the first, second, and third vaccinations in both the FLUAD* and comparator vaccines groups.

Table 1 Any (Severe[a]) Local and Systemic Reactions in Elderly Subjects ≥65 Years (Days 0-3) After One Vaccination - Pooled Studies

Reaction	Percentages of Subjects with Any (Severe[a]) Solicited Reaction	
	FLUAD*	**Comparator**
	N = 3713	**N = 1656**
Subjects with Any Solicited Local Reaction	**37**%	**30**%
Pain at injection site	26% (<1%) *N = 3712*	14% (<1%)
Temperature at injection site	18% (1%) *N = 2265*	11% (1%) *N = 1438*
Ecchymosis	3% (<1%) *N = 1272*	2% (0) N = 44
Induration	11% (1%) *N = 3712*	9% (1%) *N = 1655*
Erythema	14% (1%) *N = 3712*	14% (1%) *N = 1655*
Swelling	5% (1%) *N = 1447*	6% (1%) *N = 218*
Subjects with Any Solicited Systemic Reaction	**17%**	**12%**
Chills	3% (<1%) *N = 3712*	2% (<1%) *N = 1655*
Fatigue	6% (<1%) *N = 1493*	7% (1%) *N = 264*
Headache	6% (<1%) *N = 3712*	5% (1%) *N = 1655*
Malaise	6% (<1%) *N = 3712*	5% (<1%) *N = 1655*
Myalgia	7% (<1%) *N = 3712*	3% (<1%) *N = 1655*
Nausea	2% (<1%) *N = 2581*	2% (<1%) *N = 1655*
Rash	<1% (<1%) *N = 2230*	<1% (<1%) *N = 1365*
Sweating	3% (0) *N = 1447*	3% (<1%) *N = 218*
Arthralgia	4% (<1%) *N = 3666*	2% (<1%) *N = 1609*
Fever (≥38°C/≥40°C)	1% (0) *N = 3675*	<1% (0) *N = 1652*

[a]Defined as ecchymosis, erythema, induration, and swelling >50mm; temperature at injection site "hot"; rash "urticaria"

Table 2 Any (Severe[a]) Local and Systemic Reactions in Elderly Subjects ≥65 Years (Days 0-3) Who Received Two Consecutive FLUAD* Vaccinations One Year Apart, by Vaccination

	Percentages of Subjects with Any (Severe[a]) Solicited Reaction			
	1st Vaccination		2nd Vaccination	
	FLUAD* N=487	Comparator N=329	FLUAD* N=487	Comparator N=329
Solicited Local Reactions				
Pain at injection site	19% (1%)	7% (0)	27% (1%)	21% (<1%)
Temperature at injection site	6% (2%)	4% (1%)	15% (3%)	12% (2%)
Induration	9% (1%)	6% (1%)	13% (1%)	10% (<1%)
Erythema	9% (1%)	6% (0)	23% (2%)	20% (3%)
Solicited Systemic Reactions				
Chills	4% (<1%)	4% (<1%)	3% (0)	2% (0)
Fatigue	15% (0) *N=39*	0 *N=35*	0 *N=39*	3% (0) *N=35*
Headache	5% (<1%)	5% (<1%)	8% (0)	5% (0)
Malaise	7% (<1%)	6% (0)	8% (0)	6% (<1%)
Myalgia	4% (<1%)	2% (<1%)	3% (0)	2% (0)
Nausea	3% (0)	2% (0)	2% (0)	3% (<1%)
Rash	<1% (<1%) *N=306*	<1% (0) *N=222*	<1% (<1%)	<1% (0)
Arthralgia	2% (<1%) *N=448*	1% (<1%) *N=294*	1% (0)	2% (0)
Fever (≥38°C/≥40°C)	1% (0)	0	1% (0)	1% (0)

[a]Severe defined as: induration, erythema and swelling >50mm; temperature at injection site "hot"; rash "urticaria"

Table 3 Any (Severe[a]) Solicited Local and Systemic Reaction in Elderly Subjects ≥65 Years (Days 0-3) Who Received Three Consecutive FLUAD* Vaccinations One Year Apart, by Vaccination

Reaction	Percentages of Subjects with Any (Severe[a]) Solicited Reaction					
	1st Vaccination		2nd Vaccination		3rd Vaccination	
	FLUAD* N=149	Comp. N=87	FLUAD* N=150	Comp. N=87	FLUAD* N=150	Comp. N=87
Solicited Local Reactions						
Pain at injection site	28% (1%)	5% (0)	29% (1%)	15% (0)	28% (1%)	16% (0)
Temperature at injection site	4% (1%)	5% (0)	7% (1%)	2% (1%)	12% (1%)	7% (0)
Induration	8% (0)	5% (0)	12% (1%)	6% (0)	13% (1%)	6% (0)
Erythema	9% (0)	6% (0)	14% (1%)	7% (1%)	22% (3%)	9% (0)
Solicited Systemic Reactions						
Chills	4% (0)	6% (1%)	1% (0)	2% (0)	3% (0)	0
Fatigue	17% (0)	0	0 *(N=35)*	3%*(N=32)*	- *(N=0)*	- *(N=0)*
Headache	4% (0)	2% (0)	8% (0)	5% (0)	4% (1%)	3% (0)
Malaise	7% (0)	3% (0)	5% (0)	3% (0)	7% (0)	3% (0)
Myalgia	3% (0)	1% (1%)	5% (0)	2% (0)	1% (0)	2% (0)
Nausea	2% (0)	0	3% (0)	2% (0)	3% (0)	2% (0)
Rash	- *(N=0)*	- *(N=0)*	0 *(N=115)*	0 *(N=55)*	0	0
Arthralgia	2% (0)	2% (2%)	1% (0)	3% (0)	1% (0)	3% (0)
Fever (≥38°C)	0	0	1% (0)	0	1% (0)	0

[a]Severe defined as: induration, erythema and swelling >50mm; temperature at injection site "hot"; rash "urticaria"; Comp.= comparator vaccine

Post-Market Adverse Drug Reactions

FLUAD* was first licensed in Italy in 1997. The authorization was extended to other European Union countries through a Mutual Recognition Procedure that concluded in 2000 and currently FLUAD* is registered for marketing authorization in many countries worldwide. The initial formulation contained the preservative thimerosal, and thimerosal was also used in the manufacturing process. Since 2003 FLUAD* has been thimerosal-free (see Pharmaceutical Information section).

The post-marketing experience with FLUAD* is extensive. Because post-marketing reporting is voluntary and from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

The adverse events described below have been included because: a) they represent reactions that are known to occur following immunizations generally or influenza immunizations specifically; b) they are potentially serious; or c) of the frequency of reporting. The following additional adverse reactions have been the subject of spontaneous reports during post-approval use of FLUAD* since 2003.

General disorders and administration site conditions:

Local injection site reactions including redness, swelling, pain at the injection site, ecchymosis, induration.

Immune system disorders:

Allergic reactions in rare cases leading to shock.

Vascular disorders:

Vasculitis (in rare cases associated with transient renal involvement).

Blood and lymphatic system disorders:

Thrombocytopenia (including very rare severe cases, <0.01%, with platelet counts less than 5,000 per mm^3)

Nervous system disorders:

Neuralgia, paraesthesia, convulsion, myelitis (including encephalomyelitis and transverse myelitis), neuritis and Guillain-Barré Syndrome.

Skin and subcutaneous tissue disorders:

Generalized skin reactions including pruritus, urticaria, and non-specific rash.

DRUG INTERACTIONS

Overview

No interaction between FLUAD* and other vaccines or medication are known.

Drug-Drug Interactions

FLUAD* may be given at the same time as other vaccines. FLUAD* should not be mixed with any other vaccine in the same syringe. Immunization should be carried out on separate limbs. It should be noted that any adverse reactions may be intensified.
Although a possible interaction has been suggested in the literature between influenza vaccination and the use of warfarin and theophylline, clinical studies have not shown any adverse effects attributable to these drugs in people receiving influenza vaccine. There were no studies designed to evaluate the drug interactions with FLUAD*.

The immunological response may be diminished if the patient is undergoing immunosuppressant treatment.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Adults 65 years of age and older: a single dose of 0.5 mL should be administered intramuscularly.

FLUAD* should under no circumstances be administered by any other route than intramuscularly.

Administration

Gently shake the contents of each syringe to aid inspection for the presence of particulate matter. After shaking, the normal appearance of FLUAD* is a milky-white suspension.

If there are visible particles, allow the vaccine to come to room temperature and shake before use (FLUAD***** can be kept at room temperature (20º-25ºC) for up to 2 hours as a holding time before injection).

Do not use the vaccine if particles remain, if it is discoloured, or if it has been frozen.

Before immunization, the skin over the site to be injected should be cleansed with a suitable germicide.

FLUAD* should be administered as a single 0.5 mL intramuscular injection preferably in the region of the deltoid muscle of the upper arm. The vaccine should not be injected in the gluteal region or areas where there may be a major nerve trunk.

FLUAD* should under no circumstances be administered by any other route than intramuscularly.

Administration with Other Vaccines

FLUAD* should not be mixed with other vaccines in the same syringe. Separate injection limbs should be used if more than one vaccine is being administered during the same visit.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

No data are available.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Influenza illness and its complications follow infection with influenza viruses. Global surveillance of influenza identifies yearly antigenic variants. For example, since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation. Specific levels of hemagglutination inhibition (HI) antibody titers induced by vaccination with inactivated influenza virus vaccine have not been correlated with protection from influenza illness. Some studies of influenza infection, including human challenge studies following vaccination, have suggested that HI antibody titers ranging from 1:15 to 1:65 may be associated with protection from illness in 50% of subjects and protection from illness is increased with higher titers (CBER Guidance, May 2007).

Antibody against one influenza virus type or subtype may confer limited or no protection against another. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and the reason for the usual change of one or more new strains in each year's influenza vaccine. Therefore, inactivated influenza vaccines are standardized to contain the hemagglutinin of influenza virus strains (typically two type A and one type B), representing the influenza viruses likely to be circulating in Canada during the upcoming flu season, on the basis of the recommendations from the World Health Organization (WHO) and the National Advisory Committee on Immunization (NACI).

Annual revaccination with the current vaccine is recommended because immunity declines during the year after vaccination, and because circulating strains of influenza virus change from year to year (MMWR).

Pharmacodynamics

The antibody response to FLUAD* is increased when compared to the response to vaccines without adjuvant, and is most pronounced for B and A/H3N2 influenza antigens.Seroprotection is generally obtained within 2 to 3 weeks after vaccination.

This increased response is seen particularly in elderly subjects with low pre-immunization 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 immunization with FLUAD*

Consistent numerically higher antibody titers after immunization with FLUAD* have also been observed against homologous and heterovariant strains, antigenically different from those

included in the vaccine and the difference was statistically significant for some strains and/or some endpoints, as compared to the comparator.

Duration of Effect

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

STORAGE AND STABILITY

Store FLUAD* between 2°C and 8°C. Do not freeze. Do not use if vaccine has been frozen. Protect from light. Do not use vaccine after expiration date.

FLUAD* can be administered following a 2 hour exposure at temperatures between 8° and 25°C. This is not, however, a recommendation for storage.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

FLUAD* is a sterile milky-white suspension for intramuscular injection in 1 mL prefilled syringes containing a 0.5 mL dose.

Composition

Each 0.5 mL dose contains

- Active Ingredients:

- influenza virus haemagglutinin (HA) and neuraminidase (NA) from each of the following 3 strains:

A/California/7/2009 (H1N1)pdm09-like virus; 15 µg (HA)

A(H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011; 15 µg (HA)

and B/Massachusetts/2/2012-like virus; 15 µg (HA)

- *adjuvant:* MF59C.1 which is an proprietary adjuvant:

squalene	9.75 mg
polysorbate 80	1.175 mg
sorbitan trioleate	1.175 mg
sodium citrate	0.66 mg
citric acid	0.04 mg
water for injection	

- Other Ingredients:

Excipients:

sodium chloride	4.00 mg
potassium chloride	0.10 mg
potassium dihydrogen phosphate	0.10 mg
disodium phosphate dihydrate	0.67 mg
magnesium chloride hexahydrate	0.05 mg
calcium chloride dihydrate	0.06 mg
water for injection	to volume

Manufacturing Process Residuals:

The vaccine may contain trace amounts of the following:
neomycin (trace)
kanamycin (trace)
ovalbumin (egg protein, residual)
formaldehyde (residual)
cetyltrimethylammonium bromide (CTAB) (residual)
barium (residual)

The syringe plunger does not contain latex and FLUAD* is considered safe for use in persons with latex allergies.

Packaging

FLUAD* is supplied in packages containing one or ten single dose prefilled glass syringes (Type I).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Purified haemagglutinin (HA) and neuraminidase (NA) surface antigens from each of the three influenza virus strains, types A and B, recommended annually for immunization by the World Health Organisation (WHO) and the National Advisory Committee on Immunization (NACI).

Chemical name: As above

Product Characteristics

FLUAD* is a trivalent, surface antigen, inactivated influenza vaccine adjuvanted with MF59C.1.

The influenza virus strains are individually grown in the allantoic cavity of embryonated hens' eggs inoculated with a specific type of influenza virus suspension containing kanamycin and neomycin sulphate. Each of the influenza virus strains is harvested and clarified separately by centrifugation and filtration prior to inactivation with formaldehyde. The inactivated virus is concentrated and purified by zonal centrifugation. The surface antigens, hemagglutinin and neuraminidase, are obtained from the influenza virus particle by further centrifugation in the presence of cetyltrimethylammonium bromide (CTAB), a process which removes most of the internal proteins. The CTAB is removed from the surface antigen preparation.

The MF59C.1 adjuvant contained in FLUAD* is an oil-in-water emulsion composed of squalene as the oil phase, stabilised with the surfactants polysorbate 80 and sorbitan trioleate, in citrate buffer.

FLUAD* appears as a sterile, milky-white suspension for intramuscular injection in a prefilled syringe. It has been formulated to contain a total of at least 45 mcg hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 mcg HA of each of the following three influenza strains recommended for the 2013/2014 influenza season: A/California/7/2009 (H1N1)pdm09-like virus; A(H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011; and B/Massachusetts/2/2012-like virus, as recommended annually for immunization by the World Health Organisation (WHO) and the National Advisory Committee on Immunization (NACI).

CLINICAL TRIALS

Study Demographics and Trial Design

Five randomized, comparator controlled, observer blind clinical studies, were selected as pivotal studies to support the immunogenicity of FLUAD*, compared with conventional non adjuvanted influenza vaccines. Additionally, immunogenicity results of one study have been presented to support the cross reactivity to heterovariant influenza strains conferred by FLUAD*. Immune responses, specifically HI antibody titers to each virus strain in the vaccine, were evaluated in sera obtained 28 days after administration of the single dose of FLUAD*.

In the five pivotal studies and the one study investigating heterologous immune response, 212, 204, 154, 150, 448, and 46 subjects 65 years and older were enrolled to receive FLUAD*.
The demographic and baseline characteristics were well balanced both between vaccine groups in each study as well as across studies. In these studies the mean age ranged from 72 to 79.1 years, sex ratio was mostly balanced except for a prevalence (72%-75%) of females in one study, and Caucasians were the most represented ethnic group across studies. As expected in a population with a high percentage of subjects with previous influenza vaccinations (63% to 97% across studies and vaccine groups), the percentage of subjects with seroprotection at baseline was relatively high.

Study Results

Evaluation of vaccine immunogenicity was originally based on the CHMP criteria defined in the CPMP/BWP/214/96 guideline. Generally all 3 CHMP criteria were met with FLUAD* for each strain (see Table 4 below). When not all 3 criteria were met, the GMR and seroconversion/significant increase CHMP criteria were more frequently achieved with FLUAD* than with the comparator vaccine.

Table 4 CHMP Criteria Fulfilled Against Homologous Influenza Strains After One Vaccination [a] - HI assay (PP-Population)

	V7P5		V7P8		V7P17		V7P24		V7P34	
	FLUAD* (w)	AGRIFLU*	FLUAD* (w)	AGRIFLU*	FLUAD* (w)	AGRIFLU*	FLUAD* (c)	Flushield	FLUAD* (c)	AGRIFLU*
	N=94	N=97	N=100	N=99	N=147	N=150	N=140	N=140	N=211	N=106
H3N2	3/3	3/3	3/3	2/3	3/3	3/3	3/3	3/3	1/3	1/3
H1N1	3/3	2/3	1/3	1/3	3/3	2/3	2/3	2/3	3/3	2/3
B	3/3	2/3	3/3	2/3	3/3	3/3	3/3	2/3	3/3	2/3

Source: FLUAD*(w) = 'water' formulation (FLUAD*/MF59W.1); FLUAD*(c) = 'citrate' formulation (FLUAD*/MF59C.1); Note: for all studies only results with FLUAD* (single syringe) are presented; [a]i.e., on day 28.

In all five pivotal clinical trials consistent numerically higher HI antibody titers (i.e., day 28 GMT FLUAD*/comparator ratio >1) and greater percentages of subjects achieving seroconversion or significant increase in HI titres (i.e., vaccine group difference for the seroconversion rate of FLUAD*/comparator >0) for homologous strains were observed for FLUAD*. The differences were statistically significant for some strains and/or some endpoints (see Table 5 and Table 6). However, clinical relevance of the difference is unknown.

Table 5: Postvaccination GMTs and Vaccine Group Ratios - HI assay (PP-Population)

Study	Antigen	FLUAD*		Comparator		
		N	GMT (95% CI)	N	GMT (95% CI)	Vaccine Group Ratio (99.17% CI)[#]
V7P5	H3N2	94	331 (271-406)	97	161 (132-196)	2.06 (1.4-3.03) [§]
	H1N1	94	252 (214-297)	97	179 (152-211)	1.41 (1.03-1.92) [§]
	B	94	137 (115-162)	97	85 (71-100)	1.62 (1.17-2.24) [§]
V7P8	H3N2	100	121 (69-210)	99	62 (37-104)	1.94 (1.25-3.01) [§]
	H1N1	100	179 (121-265)	99	153 (106-220)	1.17 (0.86-1.6)
	B	100	77 (52-115)	99	60 (41-86)	1.3 (0.95-1.78)
V7P17	H3N2	147	276 (228-335)	150	153 (127-185)	1.81 (1.25-2.61) [§]
	H1N1	147	367 (314-429)	150	266 (228-311)	1.38 (1.03-1.85) [§]
	B	147	289 (250-335)	150	206 (178-238)	1.41 (1.07-1.86) [§]
V7P24	H3N2	140	251 (213-295)	140	204 (173-240)	1.23 (0.9-1.68)
	H1N1	140	223 (183-272)	140	217 (178-266)	1.03 (0.7-1.5)
	B	140	182 (149-222)	140	133 (109-162)	1.37 (0.94-2.0)
V7P34	H3N2	211	243 (220-267)	106	203 (177-233)	1.19 (0.95-1.5)
	H1N1	211	203 (175-235)	106	155 (126-190)	1.31 (0.93-1.85)
	B	211	168 (147-191)	106	140 (116-168)	1.2 (0.89-1.63)

2-sided 99.17% Bonferroni adjusted CI within each study for 6 comparisons (3 strains by 2 endpoints).
[§]indicate that if CI does not contain 1, i.e. statistically significant difference.

Table 6: Postvaccination SC and Vaccine Group Differences - HI assay (PP-Population)

Study	Antigen	FLUAD*		Comparator		
		N	SC (95% CI)	N	SC (95% CI)	Vaccine Group Difference (99.17% CI)[#]
V7P5	H3N2	94	83 (74-90)	97	61 (50-71)	22 (5-38) [§]
	H1N1	94	32 (23-42)	97	23 (15-32)	9 (-8-26)
	B	94	52 (42-63)	97	30 (21-40)	22 (4-40) [§]
V7P8	H3N2	100	54 (44-64)	99	28 (20-38)	26 (7-42) [§]
	H1N1	100	23 (15-32)	99	11 (6-19)	12 (-2-26)
	B	100	35 (26-45)	99	27 (19-37)	8 (-10-25)
V7P17	H3N2	147	55 (47-63)	150	36 (28-44)	19 (4-33) [§]
	H1N1	147	35 (27-43)	150	23 (17-31)	11 (-3-25)
	B	147	48 (40-57)	150	33 (25-41)	16 (1-30) [§]
V7P24	H3N2	140	56 (48-65)	140	35 (27-44)	21 (6-36) [§]
	H1N1	140	26 (19-35)	140	24 (17-32)	2 (-12-16)
	B	140	41 (32-49)	140	27 (20-35)	14 (-1-28)
V7P34	H3N2	211	23(18-30)	106	18(11-27)	5 (-8-17)
	H1N1	211	40 (33-47)	106	30 (22-40)	10 (-6-24)
	B	211	41 (34-48)	106	25 (17-34)	16 (1-30) [§]

SC = seroconversion or significant increase;,
# 2-sided 99.17% Bonferroni adjusted CI within each study, for 6 comparisons (3 strains by 2 endpoints).
[§] indicate that if CI does not contain 0, i.e. statistically significant difference.

Postvaccination GMTs and seroconversion rates for heterovariant strains were observed to be consistently higher for FLUAD* than for AGRIFLU*. The difference was statistically significant for some strains and/or some endpoints (see Table 7).

Table 7 GMT and Seroconversion Response to Heterovariant Influenza Strains After One Vaccination [a] – Study V7P3 - HI assay (PP-Population)

		FLUAD*	AGRIFLU*	Vaccine Group Comparisons (99.17% CI)[#]
		N=39	N=35	
H3N2	GMT (95% CI)	173 (117-256)	99 (65-150)	1.75 (0.81-3.8)
	% SC (95% CI)	79 (64-91)	46 (29-63)	34 (4-58) [§]
H1N1	GMT (95% CI)	270 (200-365)	133 (97-183)	2.03 (1.12-3.67) [§]
	% SC (95% CI)	74 (58-87)	37 (21-55)	37 (7-61) [§]
B	GMT (95% CI)	200 (153-261)	105 (79-139)	1.9 (1.12-3.24) [§]
	% SC (95% CI)	92 (79-98)	69 (51-83)	24 (0-48)

SC= seroconversion or significant increase, i.e., ≥4-fold increase in HI titer from a pre-vaccination titer ≥1:10 or a rise from <1:10 to ≥1:40 in those who were serum-negative at baseline;
[a] i.e., on day 28.
2-sided 99.17% Bonferroni adjusted CI within each study, for 6 comparisons (3 strains by 2 endpoints).
[§] indicate statistically significant difference/ratio.

Seroprotection GMR and rates for heterovariant strains were observed to be consistently higher for FLUAD* than for AGRIFLU* (see Table 8).

Table 8 Seroprotection and GMR Immune Response to Heterovariant Influenza Strains After One Vaccination [a] – Study V7P3 - HI assay (PP-Population)

		FLUAD*	AGRIFLU*
		N=39	**N=35**
H3N2	% SP (95% CI)	100 (91-100)	83 (66-93)
	GMR (95% CI)	7.86 (5.41-11)	4.08 (2.75-6.06)
H1N1	% SP (95% CI)	100 (91-100)	94 (81-99)
	GMR (95% CI)	5.32 (3.84-7.36)	2.54 (1.8-3.57)
B	% SP (95% CI)	100 (91-100)	97 (85-100)
	GMR (95% CI)	9.06 (7.08-12)	3.84 (2.96-4.99)

SP= seroprotection, i.e., HI titer ≥1:40, GMR= day 28/day 0 geometric mean titer ratio.
[a] i.e., on day 28.

TOXICOLOGY

Nonclinical Toxicology Studies

Study type, gender, and species	**Route and regimen**[a]	**Results**
Repeat dose toxicity - male and female rabbits	Two or three 0.5 mL intramuscular doses of FLUAD* two weeks apart	There were no systemic adverse effects, and FLUAD* was well tolerated locally.
Delayed contact hypersensitivity - female Guinea pigs	Intradermal 0.1 mL and topical 0.5 mL doses of FLUAD* during induction phase, and topical 0.5 mL dose of FLUAD* during challenge phase.	FLUAD* was not a skin sensitiser in Guinea pigs in this study.

[a]On a body weight basis, each dose administered to rabbits was approximately 15 times the human dose

FLUAD* has not been evaluated for reproductive and developmental toxicity, carcinogenic or mutagenic potential.

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PART III: CONSUMER INFORMATION

FLUAD*

(Influenza Virus Vaccine, surface antigen, inactivated, Adjuvanted with MF59C.1)

This leaflet is part III of a three-part "Product Monograph" published when FLUAD* was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about FLUAD*. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS VACCINE

What the vaccine is used for:

FLUAD* is an inactivated influenza virus vaccine against influenza subtypes A and B contained in the vaccine, indicated in adults 65 years of age and older.

What it does:

FLUAD* provides active immunization of persons 65 years of age and older against influenza disease, used to prevent people from developing influenza (the flu), or reduce flu symptoms.

Like other influenza vaccines FLUAD* causes the body to produce antibodies against the virus. This means that when your body is exposed to the flu virus, your body is able to defend itself. The antibodies stop the attacking virus. You cannot catch influenza from the vaccine, since it only contains portions of the virus, and not the whole live virus. Your body takes 2 to 3 weeks to produce antibodies after vaccination. Therefore, if you are exposed to influenza immediately before or after your vaccination, you could still develop the illness. The vaccine will not protect you against the common cold, even though some of the symptoms are similar to influenza. Influenza viruses change all the time, so different vaccines are made every year. To stay protected against influenza, you need to be re-vaccinated every year before the winter season.

It is particularly important for some groups of people to be vaccinated. These include people with certain medical conditions, elderly people, people who are likely to be exposed to the infection and people on certain medications. If you are in doubt as to whether you should be vaccinated, talk to your local health professionals.

FLUAD* follows the World Health Organisation (WHO) and National Advisory Committee on Immunization (NACI) recommendation for vaccination for the northern hemisphere for the 2013/2014 season.

When it should not be used:

FLUAD* should not be used where there is a history of hypersensitivity to egg proteins or other components of the vaccine, any of the excipients or in people who have had a life-threatening reaction to previous influenza vaccination. (For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph).

What the medicinal ingredients are:
Influenza virus vaccine (surface antigen, inactivated) subtypes A and B (2013/2014 season)

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

A/California/7/2009 (H1N1)pdm09-like virus;
15 micrograms HA[§]

A(H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011;
15 micrograms HA[§]

B/Massachusetts/2/2012-like virus;
15 micrograms HA[§]

Per 0.5 ml dose

[§] haemagglutinin

This vaccine complies with the WHO recommendations (northern hemisphere) for the 2013/2014 season.

What the important nonmedicinal ingredients are:

Sodium chloride, Potassium chloride, Potassium dihydrogen phosphate, Disodium phosphate dihydrate, Magnesium chloride hexahydrate, Calcium chloride dihydrate, Squalene, Polysorbate 80, Sorbitan trioleate, Sodium citrate, Citric acid and Water for Injections.

May also contain trace amounts of:

Neomycin, kanamycin, egg proteins, formaldehyde, or cetyltrimethylammonium bromide (CTAB), barium (residual),

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:

- Each 0.5 mL dose contains 15 micrograms of influenza virus haemagglutinin (HA) from each of the following 3 strains: A/California/7/2009 (H1N1)pdm09-like virus, A(H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011, and B/ Massachusetts/2/2012-like virus.

- Sterile suspension for intramuscular injection provided as one or ten single dose prefilled glass syringes (Type I).
- FLUAD* does not contain thimerosal or any other preservative.
- The syringe plunger does not contain latex and FLUAD* is considered safe for use in persons with latex allergies

WARNINGS AND PRECAUTIONS

FLUAD* should not be administered to anyone with known allergies to eggs or egg products, or any other constituent of the vaccine or to anyone who has had a life-threatening reaction to previous influenza vaccination.

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.

Immunocompromised patients may have a diminished immune response to FLUAD*.

BEFORE you use FLUAD*, talk to your doctor or pharmacist if:

• You are allergic to eggs or egg-products
• You are allergic to any of the following: kanamycin and neomycin sulphate, formaldehyde, cetyltrimethylammonium bromide, or polysorbate 80
• You have a fever, or you think you may be getting a fever
• You had a serious reaction to any flu vaccine in the past
• You have any known allergies
• You have experienced any health problems
• You are pregnant: ask your doctor for advice
• You are currently on any medication (i.e. immunosuppressant, theophylline, anticoagulants such as warfarin)

FLUAD* may be given at the same time as other vaccines.
Do not mix with any other vaccine in the same syringe.
As with any vaccine, immunization with FLUAD* may not protect 100% of individuals against influenza disease.
Immunosuppressive therapies may reduce immune response to FLUAD*.

USE IN SPECIFIC POPULATIONS

- Safety and effectiveness of FLUAD* has not been established in pregnant women and nursing mothers.
- Safety and effectiveness in children and adolescents has not been established.
- Antibody responses were lower in the geriatric population than in younger subjects.

INTERACTIONS WITH THIS VACCINE

Overview

No interaction between FLUAD* and other vaccines or medication is known.

Drug-Drug Interactions

FLUAD* may be given at the same time as other vaccines. FLUAD* should not be mixed with any other vaccine in the same syringe. Immunization should be carried out on separate limbs. It should be noted that the systemic adverse reactions may be intensified.

The immunological response may be diminished if the patient is undergoing immunosuppressant treatment.

Although a possible interaction has been suggested in the literature between influenza vaccination and the use of warfarin and theophylline, clinical studies have not shown any adverse effects attributable to these drugs in people receiving influenza vaccine. There were no studies designed to evaluate the drug interactions with FLUAD*.

PROPER USE OF THIS VACCINE

Usual dose: Adults aged 65 years and over: A single dose of 0.5 mL should be administered intramuscularly.

Immunization should be carried out by intramuscular injection only.

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

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

No data are available.

Missed Dose: Not applicable

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Vaccination with FLUAD* (influenza vaccine, surface antigen, inactivated) cannot cause influenza because the vaccine does not contain live virus. Respiratory disease after vaccination represents coincidental illness unrelated to influenza vaccination.

Occasionally people have side effects with influenza vaccines. The most common of these are fever, feeling unwell, shivering, tiredness, headache, sweating, muscle joint pain, and warmth. Skin reactions include redness, swelling, pain, ecchymosis (blue/black staining of the skin) and a hardening of the skin at the injection site and itching. These reactions will normally disappear without treatment in a day or two.

Rarely, neuralgia (nerve pain), paresthesia (numbness and tingling), convulsions (seizures), thrombocytopenia (a blood disorder) and allergic reactions (this might include but is not limited to breathing or swallowing difficulties, or swelling in the face or skin) have been reported with influenza vaccination. In rare cases, allergic reactions may lead to shock.

Very rarely, vasculitis (inflammation of blood vessels) temporarily affecting the kidneys, neurological disorders (affecting the nerves and brain), such as encephalomyelitis, and neuritis have been reported.

The most common (≥ 10%) local (injection-site) adverse reactions observed in clinical studies were injection site pain, induration, swelling, and erythema.

The most common (≥ 10%) systemic adverse reactions observed in clinical studies were headache, myalgia, and malaise.

This is not a complete list of side effects. For any unexpected effects while taking FLUAD*, *contact your doctor or pharmacist.*

HOW TO STORE IT

This product should be stored at 2°C to 8°C (in a refrigerator), not frozen. The syringe should be kept in the outer carton, thus protecting it from light.

FLUAD* can be administered following a 2 hour exposure at temperatures between 8° and 25°C. This is not, however, a recommendation for storage.

Do not use vaccine after the expiration date.

MORE INFORMATION

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects case reports on adverse events following immunization.

For health care professionals:

If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events following Immunization (AEFI) Form and send it to your local Health Unit in your province/territory.

For the General Public:

Should you experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events following Immunization (AEFI) Form.

If you have any questions or have difficulties contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada :

By toll-free telephone: 866-844-0018
By toll-free fax: 866-844-5931
Email: caefi@phac-aspc.gc.ca
Web: http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php

Mail:
The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road, A/L 6502A
Ottawa, ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice

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This document plus the full product monograph, prepared for health professionals can be found at:

http://www.novartis.ca

or by contacting the sponsor, Novartis Vaccines and Diagnostics at 1-800-363-8883

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385 Bouchard Blvd.
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