

PRESCRIBING INFORMATION

AGRIFLU*

(Influenza Vaccine, Surface Antigen, Inactivated)

Sterile Suspension for Injection

Active Immunizing Agent for the Prevention of Influenza

2011/2012 Strains: an A/California/7/2009 (H1N1)-like virus
an A/Perth/16/2009 (H3N2)-like virus
a B/Brisbane/60/2008-like virus

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*AGRIFLU is a registered trademark

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AGRIFLU*

(Influenza Virus Vaccine, Surface Antigen, Inactivated)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1 Summary Product Information

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|--------------------------------|--|--|
| Intramuscular injection | Parenteral / Each 0.5 mL pre-filled syringe contains 15µg of influenza virus haemagglutinin surface antigens from each of the three virus strains, types A and B (see DESCRIPTION) | Trace amounts of neomycin, kanamycin, egg proteins, formaldehyde, polysorbate 80, cetyltrimethylammonium bromide (CTAB). <i>For a complete listing see Dosage Forms, Composition and Packaging Section.</i> |

DESCRIPTION

AGRIFLU* is a trivalent, surface antigen, inactivated influenza virus vaccine prepared from virus propagated 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.

AGRIFLU* is a sterile clear aqueous suspension for an intramuscular use that 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 2011/2012 influenza season: A/California/7/2009 (H1N1)-like virus (H1N1); A/Perth/16/2009 (H3N2)-like virus (H3N2); and B/Brisbane/60/2008-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

AGRIFLU* is an inactivated influenza virus vaccine indicated for active immunization of persons 6 months of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine (see DOSAGE AND ADMINISTRATION and PART II CLINICAL TRIALS).

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

Vaccine should be offered to both children and adults up to and even after influenza virus activity is documented in a community.

CONTRAINDICATIONS

AGRIFLU* 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, polysorbate 80 and cetyltrimethylammonium bromide (CTAB), or in anyone who has had a life-threatening reaction to previous influenza vaccination.

Patients who are hypersensitive to AGRIFLU* or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

General

AGRIFLU* should under no circumstances be administered intravascularly.

The pre-filled syringes are single use only. If a half dose (0.25mL) is administered to infants and children, discard half the contained volume (up to the mark indicated on the syringe barrel), before injection.

Prior to administration of any dose of AGRIFLU*, 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, 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 following administration of the vaccine.

Immunization with AGRIFLU* shall be postponed in patients with febrile illness or acute infections.

As with any vaccine, immunization with AGRIFLU* may not protect 100% of individuals against influenza disease.

Hematologic

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

Immune

The immune response to AGRIFLU* in immunocompromised persons, including individuals receiving immunosuppressive therapy, may be lower than in immunocompetent individuals. It is possible that 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 AGRIFLU* should be based on careful consideration of the potential benefits and risks.

Immunization should be delayed in a patient with an active neurologic disorder, but should be considered when the disease process has been stabilized.

Special Populations

Pediatrics (≥6 months to 17 years of age):

Results of clinical studies conducted in children aged 6 months to 17 years demonstrate that AGRIFLU* was well tolerated and immunogenic. Immunogenicity and safety data are limited in 6 to 35 months old children (see PART II CLINICAL TRIALS). However, a post-marketing clinical study was initiated in 6 to 72 months-old children.

Geriatrics (≥65 years of age)

Results of clinical studies conducted in healthy elderly adults demonstrate that AGRIFLU* was well tolerated. Immune responses were generally lower in the geriatric population than in younger adult subjects, but they reached acceptable levels. (see PART II CLINICAL TRIALS)

Pregnant Women:

Based on reproductive toxicology data in rabbits, AGRIFLU* is not predicted to increase the risk of developmental abnormalities. Limited data are available from vaccinations with AGRIFLU* in pregnant women.

NACI considers influenza vaccination safe during pregnancy. NACI recommends influenza vaccination in pregnant women with high-risk conditions at any stage during pregnancy.

Nursing Women:

No data are available from vaccinations with AGRIFLU* in lactating women. Exposure to AGRIFLU* is not predicted to affect the quantity and/or quality of human milk production. AGRIFLU* is not expected to be present in human milk or to affect the breast-fed child.

Adults at Risk

NACI recommends influenza vaccination in adults with chronic health conditions.

A total of 180 adult subjects aged 18 to 60 years with underlying chronic respiratory, cardiovascular and/or metabolic diseases have received AGRIFLU* in a randomized, controlled, observer-blind clinical trial performed during 2006-2007 Northern Hemisphere influenza season. The safety profile of AGRIFLU* in this at risk population is consistent with that reported for healthy adults.

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 postmarketing experience.

Vaccination with AGRIFLU* cannot cause influenza because the vaccine does not contain live virus.

Immediate, allergic-type responses, such as hives, allergic asthma, or systemic anaphylaxis occur extremely rarely. These reactions probably result from sensitivity to some vaccine component - most likely residual egg proteins (see CONTRAINDICATIONS).

The most common AGRIFLU* adverse drug reactions are pain at the injection site, and headache. Reactions are generally mild 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 AGRIFLU* thimerosal-free formulation in adults, elderly, children and adolescents is based on data from 11 studies (five controlled and six uncontrolled studies mostly conducted for the annual strain composition update as required in European countries where AGRIFLU* is currently marketed). (see PART II CLINICAL TRIALS). In all studies solicited local (injection site) and systemic reactions were collected from subjects/subjects' parents who completed a symptom diary card for at least four days following vaccination.

Adults 18 to 64 Years of Age

Safety data for adults 18 to 64 years of age come from ten clinical trials: six open label and single arm, whereas four (Studies C, E, G and J) included an investigational vaccine as comparator. Reactogenicity data are presented individually by study in Table 2.

The most frequently reported solicited local adverse events within 4 days of vaccination were injection site pain, followed by induration, erythema, and swelling. Except for <1% of subjects reporting severe pain all solicited local adverse events were mild to moderate in intensity and generally transient.

The most frequently reported solicited systemic adverse events were headache, myalgia, malaise, and fatigue. Most reports of solicited systemic reactions were mild to moderate in intensity and

generally transient, with 2% or less of subjects reporting a severe solicited systemic adverse event across all studies.

Table 2: Percentage of Subjects 18-64 Years of Age Reporting Solicited Adverse Events in Days 1-4 After Vaccination With AGRIFLU*

| | Percentage of Subjects with Adverse Events | | | | | | | | | |
|--|--|--------------------|---------------------|--------------------|---------------------|--------------------|---------------------|--------------------|--------------------|---------------------|
| | Study A 2003-04 | Study B 2004-05 | Study C 2004-05* | Study D 2004-05 | Study E 2005-06* | Study F 2005-06 | Study G 2005-06* | Study H 2006-07 | Study I 2007-08 | Study J 2007-08* |
| | N =79 | N =67 | N =841 | N =80 | N =662 | N =64 | N =171 | N =92 | N =68 | N =460 |
| Local Reactions | | | | | | | | | | |
| Injection site Pain | 18 | 31 | 15 | 13 | 16 | 20 | 8 | 22 | 21 | 25 |
| Erythema | 0 | 9 | 15 | 11 | 11 | 3 | 18 | 1 | 4 | 6 |
| Induration | 6 | 15 | 6 | 8 | 6 | 5 | 11 | 7 | 10 | 8 |
| Swelling | 3 | 9 | 4 | 4 | 3 | 5 | 8 | 3 | 0 | 6 |
| Ecchymosis | 1 | 3 | 3 | 5 | 4 | 2 | 6 | 0 | 3 | 5 |
| Systemic Complaints | | | | | | | | | | |
| Fatigue | 6 | 13 | 11 | 10 | 7 | 6 | 11 | 11 | 4 | 10 |
| Malaise | 5 | 6 | 10 | 9 | 6 | 3 | 12 | 5 | 7 | 12 |
| Chills | 0 | 3 | 4 | 3 | 1 | 3 | 7 | 2 | 0 | 5 |
| Fever ($\geq 38^{\circ}\text{C}$) | 0 | 0 | <1 | 0 | 1 | 0 | 2 | 1 | 0 | 2 |
| Musculoskeletal and connective tissue disorders | | | | | | | | | | |
| Myalgia | 3 | 12 | 7 | 11 | 7 | 9 | 5 | 7 | 9 | 14 |
| Arthralgia | 4 | 9 | 4 | 8 | 3 | 6 | 1 | 2 | 4 | 7 |
| Nervous System Disorders | | | | | | | | | | |
| Headache | 10 | 10 | 10 | 14 | 5 | 5 | 9 | 11 | 10 | 23 |
| Skin and Subcutaneous Disorders | | | | | | | | | | |
| Sweating | 3 | 9 | 4 | 8 | 3 | 9 | 3 | 5 | 9 | 5 |

* active-controlled trials

Adults 65 Years of Age and Older

Safety data for subjects 65 years of age and older come from eight clinical trials: six open label and single arm, whereas the remaining two (Studies C and E) included an investigational vaccine as comparator.

Reactogenicity data are provided individually by study (Table 3).

The most frequently reported solicited local adverse events within 4 days of vaccination were injection site pain, followed by erythema, induration and swelling. All solicited local adverse events were mild to moderate in intensity and generally transient, with no subjects reporting severe solicited local adverse events across all studies.

The most frequently reported solicited systemic adverse events were fatigue, headache, malaise, arthralgia and sweating. Most reports of solicited systemic reactions were mild to moderate in intensity and generally transient, with 2% or less of subjects reporting a severe solicited systemic adverse event across all studies.

Table 3: Percentage of Subjects ≥ 65 Years of Age Reporting Solicited Adverse Events in Days 1-4 After Administration of AGRIFLU*

| | Percentage of Subjects with Adverse Events | | | | | | | |
|--|--|----------------------|-----------------------|----------------------|-----------------------|----------------------|----------------------|----------------------|
| | Study A 2003-2004 | Study B 2004-2005 | Study C 2004-2005* | Study D 2004-2005 | Study E 2005-2006* | Study F 2005-2006 | Study H 2006-2007 | Study I 2007-2008 |
| | N =33 | N =52 | N =483 | N =49 | N =469 | N =46 | N =32 | N =57 |
| Local Reactions | | | | | | | | |
| Injection site Pain | 0 | 6 | 3 | 6 | 5 | 0 | 9 | 5 |
| Erythema | 0 | 2 | 10 | 4 | 5 | 2 | 0 | 0 |
| Induration | 0 | 6 | 4 | 6 | 2 | 4 | 0 | 2 |
| Swelling | 0 | 8 | 2 | 4 | 1 | 2 | 0 | 0 |
| Ecchymosis | 0 | 2 | 4 | 0 | 6 | 4 | 3 | 2 |
| Systemic Complaints | | | | | | | | |
| Fatigue | 0 | 6 | 11 | 4 | 6 | 2 | 0 | 7 |
| Malaise | 0 | 2 | 8 | 6 | 6 | 7 | 3 | 4 |
| Chills | 0 | 2 | 2 | 4 | 1 | 2 | 0 | 5 |
| Fever (≥38°C) | 3 | 0 | <1 | 0 | <1 | 0 | 0 | 4 |
| Musculoskeletal and connective tissue disorders | | | | | | | | |
| Myalgia | 0 | 4 | 6 | 0 | 2 | 9 | 3 | 7 |
| Arthralgia | 0 | 2 | 5 | 6 | 3 | 9 | 0 | 12 |
| Nervous System Disorders | | | | | | | | |
| Headache | 3 | 4 | 9 | 6 | 7 | 4 | 3 | 5 |
| Skin and Subcutaneous Disorders | | | | | | | | |
| Sweating | 0 | 0 | 7 | 8 | 3 | 2 | 0 | 9 |

* active-controlled trials

Children and Adolescents (≥6 months to 17 years of age)

Safety data for the pediatric population come from two controlled studies. Reactogenicity data are presented individually by study in Table 4.

Study K was an active controlled trial conducted in previously unvaccinated young children aged ≥6 to <36 months of age who received two half vaccine doses (i.e., 7.5 µg HA/strain) 4 weeks apart.

The most frequently observed solicited local and systemic adverse events in the young children were tenderness and irritability, respectively (Table 4). Solicited local and systemic reactions were of short duration and of generally mild or moderate intensity, with few solicited adverse events reported as severe (by 1% of subjects or less).

Study J in addition to enrolling adults also included 802 pediatric and adolescent subjects who received AGRIFLU* (402 aged 3 to 18 years and 400 aged 9 to 17 years) (see CLINICAL TRIALS Section). AGRIFLU* was generally well tolerated in these age groups and the safety profile was consistent with that reported for healthy adults with pain, headache and myalgia being the most frequently reported solicited local and systemic reactions, respectively. Severe solicited local or systemic reactions were reported by 1% of subjects or less and were generally transient.

Table 4 Summary of Solicited Local and Systemic Reactions (Days 1-4) -Children and Adolescents ≥6 months to 17 years of age (Studies K and J)

| Type of Reaction | Percentages of Subjects with Adverse Events | | | | | |
|---------------------------------------|---|-----------------------|-------------|----------------------|-----------------------|---------------------------|
| | Study K 2005-2006 | | | Study J 2007-2008 | | |
| | Children 6- <36 months | | | Children 3-8 years | | Adolescents 9-17 years |
| | 1 st vac | 2 nd vacc. | | 1 st vacc | 2 nd vacc. | |
| | N=93 | N=89 | | N=402 | N=396 | N=400 |
| Local reactions | | | | | | |
| Ecchymosis | 2 | 0 | Ecchymosis | 4 | 3 | 2 |
| Erythema | 9 | 4 | Erythema | 2 | 1 | 2 |
| Induration | 0 | 1 | Induration | 2 | 3 | 7 |
| Swelling | 0 | 1 | Swelling | 5 | 3 | 7 |
| Tenderness | 19 | 17 | Pain | 17 | 14 | 29 |
| Systemic reactions^a | | | | | | |
| Change in eating habits | 10 | 9 | Headache | 6 | 3 | 13 |
| Sleepiness | 10 | 9 | Malaise | 3 | 4 | 4 |
| Irritability | 25 | 15 | Fatigue | 3 | 2 | 6 |
| Unusual crying | 4 | 3 | Myalgia | 4 | 5 | 8 |
| Vomiting | 1 | 0 | Chills | 2 | 1 | 4 |
| Diarrhoea | 2 | 6 | Arthralgia | 1 | 1 | 2 |
| Fever ≥38°C | 2 | 2 | Sweating | 1 | 1 | 1 |
| | | | Fever ≥38°C | 2 | 1 | <1 |

^acategories present/not present

Post-Market Adverse Drug Reactions

AGRIFLU* was first licensed in Italy in 1986 for use in persons 6 months of age and older. The authorization was extended to other European Union countries in 1998 and currently AGRIFLU* 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 AGRIFLU* is thimerosal-free (see Pharmaceutical Information section).

The postmarketing experience with AGRIFLU* is extensive. Because postmarketing 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 adverse reactions have been the subject of spontaneous reports during post-approval use of AGRIFLU* since 2003.

General disorders and administration site conditions:

Local injection site reactions including pain limiting limb movement, local lymphadenopathy, asthenia, and facial edema.

Immune system disorders:

Hypersensitivity reactions (including throat and/or mouth edema, anaphylaxis, and anaphylactic shock)

Vascular disorders:

Vasculitis (in rare cases associated with transient renal involvement), hot flush

Gastrointestinal disorders:

Abdominal pain

Blood and lymphatic system disorders:

Transient thrombocytopenia

Eye disorders:

Conjunctivitis, eyelid edema, eye redness

Musculoskeletal and connective tissue disorders:

Myasthenia.

Nervous system disorders:

Syncope shortly after vaccination, dizziness, neuralgia, paraesthesia, convulsion, myelitis (including encephalomyelitis and transverse myelitis), neuropathy (including neuritis and brachial plexus neuropathy), paralysis (including Bell's Palsy and other cranial nerve paralyses), Guillain Barré Syndrome

Respiratory, thoracic and mediastinal disorders:

Dyspnea, chest pain, cough, sore throat

Skin and subcutaneous tissue disorders:

Angioedema, erythema multiforme, pruritus, urticaria, rash (including non-specific, maculopapular, and vesiculobulbous), leucocytoclastic vasculitis

DRUG INTERACTIONS

Overview

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

Drug-Drug Interactions

AGRIFLU* may be given at the same time as other vaccines. AGRIFLU* should not be mixed with any other vaccine in the same syringe. Immunisation 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.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Children from 6 to 35 months: Children in this age group may receive one intramuscular dose of 0.25 mL. For children in this age group who have not previously been vaccinated, a second intramuscular dose should be given after an interval of at least 4-weeks.

Children from 3 to 8 years: Children in this age group should receive a single intramuscular dose of 0.5 mL if they have been vaccinated previously with any influenza vaccine. For children who have not previously been vaccinated, a second intramuscular dose of 0.5 mL should be given with an interval of at least 4 weeks.

Children from 9 years and Adults: A single intramuscular dose of 0.5 mL should be administered.

Administration

Shake the contents of each syringe to aid inspection for the presence of particulate matter. If this condition exists, do not use the contents. Do not use the vaccine if it has been frozen.

If half a dose (0.25 ml) is to be administered, discard half the contained volume (up to the mark indicated on the syringe barrel), before injection.

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

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

Do not inject intravascularly. AGRIFLU* should be administered by intramuscular injection. The recommended site of vaccination is the deltoid muscle for adults and older children, and the anterolateral aspect of the thigh for infants and young children. The vaccine should not be injected in the gluteal region or areas where there may be a major nerve trunk.

Administration with Other Vaccines

AGRIFLU* 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. |
|--|

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. In some human studies, HI antibody titers of 1:40 or greater have been associated with protection from influenza illness in up to 50% of subjects.

Antibody against one influenza virus type or subtype confers 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.

Pharmacodynamics

Seroprotection is generally obtained within 2 to 3 weeks after vaccination.

Duration of Effect

The duration of post vaccination immunity to homologous strains or to strains closely related to the vaccine strains varies. Data from clinical studies with AGRIFLU* indicated that the acceptable level of immune response was maintained up to 12 months after vaccination.

STORAGE AND STABILITY

Store AGRIFLU* between +2°C and +8°C. Do not freeze. Protect from light. Under the above storage conditions, the recommended shelf-life for AGRIFLU* is 1 year. Do not use vaccine after expiration date.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

AGRIFLU* is a sterile clear aqueous suspension for intramuscular injection supplied in 0.5 mL dose pre-filled syringes.

Composition

Active Ingredients:

Each 0.5 mL dose contains:

15 µg per strain of haemagglutinin of influenza virus surface antigens, of each strain listed below:

A/California/7/2009 (H1N1)-like virus;

A/Perth/16/2009 (H3N2)-like virus;

and B/Brisbane/60/2008-like virus.

Other Ingredients

Excipients:

| | |
|--------------------------------|-----------|
| Sodium chloride | 4.0 mg |
| potassium chloride | 0.1 mg |
| potassium dihydrogen phosphate | 0.1 mg |
| disodium phosphate dihydrate | 0.66 mg |
| magnesium chloride | 0.05 mg |
| calcium chloride | 0.06 mg |
| water for injection | to volume |

Manufacturing Process Residuals

The vaccine may contain trace amounts of the following:

neomycin (trace)

kanamycin, (trace)

egg proteins (residual)

ovalbumin (residual)

formaldehyde (residual)

polysorbate 80 or cetyltrimethylammonium bromide (CTAB) (residual)

barium (residual)

citrates (residual)

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

Packaging

AGRIFLU* is supplied in packages containing one or ten single dose pre-filled glass syringes (Type I).

The syringe may be fitted alternatively with a Luer Lock system.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

| | |
|----------------|---|
| Proper name: | Influenza virus vaccine (Surface antigen, inactivated) |
| Chemical name: | Trivalent bulk containing purified haemagglutinin (HA) and neuraminidase (NA) surface antigens from each of the three influenza virus strains, types A and B, recommended annually (see Product Characteristics below). |

Product Characteristics

AGRIFLU* is a trivalent, surface antigen, inactivated influenza vaccine prepared from virus propagated 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.

AGRIFLU* is a sterile, clear aqueous suspension for intramuscular injection that has been formulated to contain a total of at least 45 mcg hemagglutinin (HA) per 0.5mL dose in the recommended ratio of 15 mcg HA of each of the following three influenza strains recommended for the 2011/2012 influenza season: A/California/7/2009 (H1N1)-like virus (H1N1); A/Perth/16/2009 (H3N2)-like virus (H3N2); and B/Brisbane/60/2008-like virus, as recommended annually for immunisation by the World Health Organisation (WHO) and the National Advisory Committee on Immunization (NACI).

AGRIFLU* is provided in a single dose, pre-filled syringe.

Sodium chloride, potassium chloride, potassium dihydrogen phosphate, disodium phosphate dihydrate, magnesium chloride hexahydrate, calcium chloride dihydrate, and water for injection are present as excipients.

AGRIFLU* contains no thimerosal or other preservative. No thimerosal is used during the manufacture of AGRIFLU*.

CLINICAL TRIALS

Study Demographics and Trial Design

The safety and immunogenicity profile of AGRIFLU* thimerosal-free formulation in adults, elderly, children and adolescents is based on data from 11 studies (Table 5).

Table 5: Summary of Subjects' Demographics for Clinical Trials

| Study Code | Trial Design | Dosage, route of administration | Number of subjects enrolled* | Age Range | Gender Male/Female (n) |
|----------------------------|-------------------------------|---|---------------------------------|--|---------------------------------------|
| Study A 2003-04 | open-label | 0.5 mL, IM | n=79 n=33 | 18-64 years ≥65 years | 34/45 18/15 |
| Study B 2004-05 | open-label | 0.5 mL, IM | n=67 n=52 | 18-64 years ≥65 years | 27/40 30/22 |
| Study C 2004-05 | randomized, observer blind | 0.5 mL, IM | n=841 n=483 | 18-64 years ≥65 years | 357/484 221/262 |
| Study D 2004-05 | open-label | 0.5 mL, IM | n=81 n=49 | 18-64 years ≥65 years | 27/54 23/26 |
| Study E 2005-06 | randomized, observer blind | 0.5 mL, IM | n=662 n=469 | 18-64 years ≥65 years | 269/393 199/270 |
| Study F 2005-06 | open-label | 0.5 mL, IM | n=64 n=46 | 18-64 years ≥65 years | 24/40 21/25 |
| Study G 2005-06 | randomized, observer blind | 0.5 mL, IM | n=171 | 18-64 years | 63/108 |
| Study H 2006-07 | open-label | 0.5 mL, IM | n=92 n=32 | 18-64 years ≥65 years | 31/61 18/14 |
| Study I 2007-08 | open-label | 0.5 mL, IM | n=68 n=57 | 18-64 years ≥65 years | 21/47 31/26 |
| Study J 2007-08 | randomized, observer blind | 0.5 mL, IM 2 doses 4 weeks apart (children 3 to 8 years of age) 0.5 mL, IM Single dose in adolescents and adults (aged 9 years and above) | n=402 n=400 n=460 | 3-8 years 9-17 years 18-64 years | 230/172 178/222 167/293 |
| Study K 2005 | randomized, observer blind | 0.25 mL, IM 2 doses 4 weeks apart | n=93 | 6 to < 36 months | 44/49 |

* Number of subjects enrolled in the AGRIFLU* vaccine group

Immunogenicity results as measured by the HI assay from four studies covering the entire age indication (i.e., adults aged 18-64 years, elderly aged ≥ 65 years, and children aged ≥ 6 months) using the current thimerosal-free AGRIFLU* formulation are presented below (Table 6). Immune responses, specifically HI antibody titers to each virus strain in the vaccine formulation, were evaluated in sera obtained 21 days after administration of the single dose (children 9-17 years of age, adults, elderly) or the second dose (children ≥ 6 to < 36 months and 3 to 8 years) of AGRIFLU*.

Study Results

Table 6 Summary of Immunogenicity Results

| Strain ^a | | Subjects 6-36 Months | Subjects 3-8 Years | Subjects 9-17 Years | Subjects 18-64 years | | | Subjects ≥ 65 years |
|---------------------|-----------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| | | Study K 2005/2006 (Day 50) | Study J 2007/2008 (Day 50) | Study J 2007/2008 (Day 22) | Study J 2007/2008 (Day 22) | Study C 2004/2005 (Day 22) | Study G 2005/2006 (Day 22) | Study C 2004/2005 (Day 22) |
| | | (N=79) | (N=296) | (N=393) | N=424 | N=837 | N=168 | N=481 |
| A/H1N1 | Seroprotection ^b | 43 (32-55) | 97 (94-99) | 99 (97-100) | 93 (90-95) | 90 (88-92) | 95 (91-98) | 85 (82-88) |
| | Seroconversion ^c | 43 (32-55) | 95 (91-97) | 92 (88-94) | 74 (69-78) | 65 (61-68) | 77 (70-83) | 55 (51-60) |
| | GMR ^d | 4.66 (3.68-5.9) | 20 (18-23) | 28 (24-32) | 12 (10-14) | 9.63 (8.62-11) | 16 (13-20) | 5.6 (4.94-6.35) |
| A/H3N2 | Seroprotection ^b | 76 (65-85) | 100 (99-100) | 100 (99-100) | 96 (94-98) | 99 (98-99) | 96 (92-99) | 98 (96-99) |
| | Seroconversion ^c | 76 (65-85) | 86 (82-90) | 67 (62-72) | 72 (68-76) | 65 (61-68) | 88 (82-93) | 64 (60-69) |
| | GMR ^d | 11 (9.02-14) | 11 (9.55-13) | 6.25 (5.46-7.15) | 9.93 (8.58-11) | 7.36 (6.68-8.12) | 17 (14-21) | 8.35 (7.3-9.55) |
| B | Seroprotection ^b | 28 (18-39) | 85 (80-89) | 93 (90-95) | 91 (87-93) | 90 (87-92) | 88 (82-92) | 90 (87-93) |
| | Seroconversion ^c | 28 (18-39) | 83 (78-87) | 81 (76-84) | 77 (72-81) | 79 (76-82) | 70 (63-77) | 74 (69-77) |
| | GMR ^d | 3.05 (2.42-3.84) | 15 (13-18) | 13 (11-15) | 12 (10-13) | 11 (10-12) | 8.29 (6.86-10) | 9.18 (8.17-10) |

^a The four clinical studies were conducted over three influenza seasons and AGRIFLU* was formulated with the influenza virus strains recommended by the WHO for each season; ^b Seroprotection = the percentage of subjects achieving a HI antibody titer $\geq 1:40$; ^c Seroconversion = subjects with a prevaccination (baseline) HI titer $< 1:10$ and postvaccination HI titer $\geq 1:40$; Significant Increase = subjects with a prevaccination HI titer $\geq 1:10$ and a ≥ 4 -fold increase in postvaccination HI antibody titer; ^d GMR = post-vaccination/pre-vaccination geometric mean titer (GMT) ratio.

A summary of the immunogenicity criteria for evaluation of influenza vaccines according to the European Committee for Medicinal Products for Human Use (CHMP) and the US Center for Biologics Evaluation and Research (CBER) is provided below (Table 7).

Table 7 CHMP (European) and CBER (US) Criteria for Evaluation of Influenza Vaccines

| CHMP Criteria | Adults 18–60 Years | Adults ≥61 Years |
|---|------------------------------------|-------------------------|
| Seroprotection ^a | >70% | >60% |
| Geometric Mean Ratio ^b | >2.5 | >2.0 |
| Seroconversion or significant increase ^c | >40% | >30% |
| CBER Criteria | Subjects Less Than 65 Years | Adults ≥65 Years |
| Lower limit of the two-sided 95% CI for Seroprotection ^a | ≥70% | ≥60% |
| Lower limit of the two-sided 95% CI for Seroconversion ^d | ≥40% | ≥30% |

^aSeroprotection = the percentage of subjects achieving a HI antibody titer ≥40; ^bGMR = postvaccination/prevaccination geometric mean titer (GMT) ratio; ^cSeroconversion = subjects with a prevaccination (baseline) HI titer <10 and postvaccination HI titer ≥40; Significant Increase = subjects with a prevaccination HI titer ≥10 and a ≥4-fold increase in postvaccination HI antibody titer; ^dCBER Seroconversion definition corresponds to that of CHMP seroconversion/significant increase, i.e. subjects with either a prevaccination (baseline) HI titer <10 and postvaccination HI titer ≥40 or with a prevaccination HI titer ≥10 and a ≥4-fold increase in postvaccination HI antibody titer.

Both seroprotection and seroconversion CBER criteria were met against all three viral strains for AGRIFLU* in all studies in adolescents 9 to 17 years of age, adults 18 to 64 years of age and adults ≥65 years of age. In the population of children 3 to 8 years of age, both CBER criteria were met against all three viral strains after receiving two full vaccine doses.

In the younger children, aged ≥6 to <36 months, the requirement that at least one CHMP criterion was met for each viral strain was fulfilled. Concerning CBER criteria, for the strains used in the 2005/2006 influenza season, only seroconversion rate for one strain (A/H3N2) was met. Variable responses to influenza vaccines are known to exist from season to season. As with other influenza vaccines, lower immune responses have been noted in pediatric subjects compared to adults and adolescents.

For safety data, see Part I, ADVERSE REACTIONS.

TOXICOLOGY

Nonclinical Toxicology Studies

Table 8 Summary of Nonclinical Toxicology Studies

| Study type, gender, and species | Route and regimen^a | Results |
|---|--|--|
| Repeat dose toxicity - male and female rabbits | Two 0.5 mL intramuscular doses of AGRIFLU* one or two weeks apart | There were no systemic adverse effects, and AGRIFLU* was well tolerated locally. |
| Reproductive & developmental toxicity - female rabbits | Three 0.5 mL intramuscular doses of AGRIFLU* before mating, and two additional 0.5 mL doses during gestation | No systemic toxicity in maternal rabbits. AGRIFLU* was not associated with embryofetal or developmental toxicity, or teratogenicity. A trend toward a lower gestation index and fewer animals with surviving litters in the AGRIFLU* groups compared to control groups did not reach statistical significance, and was not considered to be related to toxicity of the vaccine. The clinical relevance, if any, of this finding is not known because, on a body weight basis, each dose administered to rabbits was approximately 15 times the human dose, and studies in pregnant women have not been conducted. |

^aOn a body weight basis, each dose administered to rabbits was approximately 15 times the human dose

AGRIFLU* has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility.

REFERENCES

- 1 National Advisory Committee on Immunization (NACI). Statement on seasonal trivalent inactivated influenza vaccine (TIV) for 2010-2011. *CCDR* 2010; 36 (ACS-6): 1-49.
- 2 National Advisory Committee on Immunization: Canadian Immunization Guide, Seventh ed. Her Majesty the Queen in Right of Canada represented by the Minister of Public Works and Government Services Canada; 2006. p.80-9, 107-46, 209-20.
- 3 Advisory Committee on Immunization Practices (ACIP) 2010. Prevention and Control of Influenza with Vaccines. *MMWR* 2010; 59 (RR-8): 1-62.
- 4 Canada Communicable Disease Report (CCDR), November 15, 2001; vol.27.
- 5 Colombo et al., *Rev. Epidemiol. Santé Publique* 2001; 49 (2): 157-162.
- 6 Glathe H., Lange W. Influenza Vaccination in Older Patients *Drugs Aging* 1995; 6 (5): 368-387.
- 7 Gross P.A., Hermogenes A.W., Sacks H.S., et.al. The Efficacy of Influenza Vaccine in Elderly Persons - A Meta-analysis and Review of the Literature. *Ann Intern Med* 1995; 123 (7): 518-527.
- 8 FDA Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines. CBER, May 2007.
- 9 Hamdy RC, Micklewright M, Beecham VF, Moore SW. Influenza vaccine may enhance theophylline toxicity. A case report and review of the literature. *Journal of the Tennessee Medical Association* 1995; 88: 463-4.
- 10 Monto S.A. Influenza: Quantifying Morbidity and Mortality. *Am J Med* Jun 1987; 82 (6A): 20-25.
- 11 Spila-Alegiani et al., Reactogenicity in the elderly of nine commercial influenza vaccines: results from the Italian SVEVA study. *Vaccine* 1999; 17: 1898-1904.
- 12 Souto JC, Oliver A, Montserrat I, Mateo J, Sureda A, Fontcuberta J. Influenza immunization is a safe procedure in patients undergoing long-term anticoagulation. *Arch Intern Med* 1996; 156 : 1589-92.
- 13 Committee for Proprietary Medicinal Products (CPMP). Note for guidance on harmonisation of requirements for influenza vaccines. CPMP/BWP/214/96 12 March 1997.
- 14 Jefferson T et al., Assessment of the efficacy and effectiveness of influenza vaccines in healthy children: systematic review. *Lancet* 2005; 365:773-80.

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