PRODUCT MONOGRAPH

AGRIFLU®

(Influenza Vaccine, Surface Antigen, Inactivated)

ATC: J07BB02

Sterile Suspension for Injection

Active Immunizing Agent for the Prevention of Influenza

2017/2018 Strains: an A/Michigan/45/2015 (H1N1)pdm09-like virus
an A/Hong Kong/4801/2014 (H3N2) (H3N2)-like virus
a B/Brisbane/60/2008-like virus

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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 contains 15 mcg of influenza virus haemagglutinin surface antigens from each of the three virus strains, types A and B (see DESCRIPTION)	Thimerosal (multi dose vial presentation only) and trace amounts of neomycin, kanamycin, egg proteins, formaldehyde, polysorbate 80, cetyltrimethylammonium bromide (CTAB). *For a complete listing see Dosage Forms, Composition and Packaging Section.*

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. Thimerosal is added as a preservative in the multi-dose vial presentation only.

AGRIFLU® is a sterile clear aqueous suspension for an intramuscular use that has been formulated to contain least 15 mcg HA/0.5 mL dose of each of the following three influenza strains recommended for the 2017/2018 influenza season: A/Michigan/45/2015 (H1N1)pdm09-like virus (A/Singapore/GP1908/2015 IVR-180 (H1N1)); A/Hong Kong/4801/2014 (H3N2) (H3N2)-like virus (A/Hong Kong/4801/2014 NYMC X-263B (H3N2)); and B/Brisbane/60/2008-like virus (B/Brisbane/60/2008), 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.

The 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, thimerosal, and to eggs, egg 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 (0.25 mL) 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.

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.

In September 2011, NACI recommended that children 6 to 35 months of age should be given a full dose (0.5 mL) of trivalent inactivated influenza vaccine (TIV) instead of the previously recommended half dose (0.25 mL). This NACI recommendation applies whether the child is being given one dose of TIV or a two dose series.

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® 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 (≥38ºC)	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 (≥38ºC)	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
	1st vac	2nd vacc.		1st vacc	2nd 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 ≥38ºC	2	2	Sweating	1	1	1
			Fever ≥38ºC	2	1	<1

[a]categories 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 the AGRIFLU® pre-filled syringe presentation 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, facial edema, injection-site cellulitis-like reaction (some cases of swelling, pain, and redness extending more than 10 cm and lasting more than 1 week), and extensive swelling of injected limb lasting more than one week.

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:

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

Eye disorders:

Conjunctivitis, eyelid edema, eye redness

Musculoskeletal and connective tissue disorders:

Myasthenia.

Nervous system disorders:

Presyncope, 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

The recommended dosage schedule is presented in Table 5.

Table 5: Recommended Influenza Vaccine Dosage, by Age Group

Age Group	Dose	No. of Doses
6 to 35 months	0.25 mL[a] or 0.5 mL[b]	1 or 2[c]
3 to 8 years	0.5 mL	1 or 2[c]
≥9 years	0.5 mL	1

[a] In clinical studies conducted by Novartis, children 6 to 35 months of age received 0.25 mL dose.

[b] NACI recommends that children 6 to 35 months of age should be given a full dose (0.5 mL) of influenza vaccine.

[c] Previously unvaccinated children 6 months to <9 years of age should be given 2 doses at least 4 weeks apart.

Administration

Shake each syringe or vial to aid inspection for the presence of particulate matter before administering the vaccine and shake the multi-dose vial each time before withdrawing a dose of vaccine. After shaking, the normal appearance of AGRIFLU® is a clear liquid.

If there are visible particles, allow the vaccine to come to room temperature and shake before use (AGRIFLU® 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.

Pre-filled syringe:
If half a dose (0.25 mL) is to be administered using the pre-filled syringe, discard half the contained volume (up to the mark indicated on the syringe barrel) before injection.

Multi-dose vial:
The multi-dose vial must be used within 28 days from the initial removal of the first dose (first needle puncture into the vial) and between uses, return the multi-dose vial to the recommended storage conditions between 2° and 8°C. The number of needle punctures should not exceed 10 per multi-dose vial. A separate sterile syringe and needle must be used for each injection to prevent transmission of infectious agents from one person to another. It is recommended that small syringes (0.5 mL or 1 mL) should be used to minimize any product loss.

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.

Do not inject air bubble in syringe.

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.

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

The multi-dose vial must be used within 28 days from the initial removal of the first dose (first needle puncture into vial) and between uses, the multi-dose vial should be returned to the recommended storage conditions. The number of needle punctures should not exceed 10 per multi-dose vial.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

AGRIFLU® is a sterile clear aqueous suspension for intramuscular injection.

Composition

Active Ingredients:
Each 0.5 mL dose contains:

15 micrograms (mcg) per strain of haemagglutinin of influenza virus surface antigens, of each strain listed below:
A/Michigan/45/2015 (H1N1)pdm09-like virus (A/Singapore/GP1908/2015 IVR-180 (H1N1));
A/Hong Kong/4801/2014 (H3N2)-like virus (A/Hong Kong/4801/2014 NYMC X-263B (H3N2));
and B/Brisbane/60/2008-like virus (B/Brisbane/60/2008).

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 hexahydrate	0.05 mg
calcium chloride dihydrate	0.06 mg
water for injection	to volume
thimerosal (multi-dose vial only)	50 mcg

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 and vial stopper do not contain latex. AGRIFLU® is considered safe for use in persons with latex allergies.

Packaging

AGRIFLU® is supplied without needles in packages of:

One 0.5 mL single dose pre-filled syringe (Type 1)
Ten 0.5 mL single dose pre-filled syringes (Type 1)
The syringe may be fitted alternatively with a Luer Lock system

The syringe barrel contains a mark at 0.25mL to aid in discarding half the contained volume when a half dose is to be administered.

One 5.0 mL multi-dose glass vial (Type 1)
Ten 5.0 mL multi-dose glass vials (Type 1)
The vial is closed with a Type 1, grey, siliconized, bromobutyl stopper.

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. Thimerosal is added as a preservative in the multi-dose vial presentation only.

AGRIFLU® is a sterile, clear aqueous suspension for intramuscular injection that has been formulated to contain at least 15 mcg HA/0.5 mL dose of each of the following three influenza strains recommended for the 2017/2018 influenza season: A/Michigan/45/2015 (H1N1)pdm09-like virus (A/Singapore/GP1908/2015 IVR-180 (H1N1)); A/Hong Kong/4801/2014 (H3N2)-like virus (A/Hong Kong/4801/2014 NYMC X-263B (H3N2)); and B/Brisbane/60/2008 -like virus (B/Brisbane/60/2008), as recommended annually for immunisation by the World Health Organisation (WHO) and the National Advisory Committee on Immunization (NACI).

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

CLINICAL TRIALS

Study Demographics and Trial Design

The safety and immunogenicity profile of AGRIFLU® in adults, elderly, children and adolescents is based on data from 11 studies (Table 6).

Table 6: 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 AGRIFLU® formulation are presented below (Table 7). 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 7 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 ≥1:40; [c] Seroconversion = subjects with a prevaccination (baseline) HI titer <1:10 and postvaccination HI titer ≥1:40; Significant Increase = subjects with a prevaccination HI titer ≥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 8).

Table 8 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%

[a] Seroprotection = the percentage of subjects achieving a HI antibody titer ≥40; [b] GMR = postvaccination/prevaccination geometric mean titer (GMT) ratio; [c] Seroconversion = 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; [d] CBER 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 9 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.

[a]On 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.

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PART III: CONSUMER INFORMATION

AGRIFLU®

(Influenza Virus Vaccine, surface antigen, inactivated)

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

ABOUT THIS MEDICATION

What the medication is used for:

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 B contained in the vaccine.

What it does:

AGRIFLU® provides active immunization of persons 6 months of age and older against influenza disease, used to prevent people from developing influenza (the flu), or reduce flu symptoms.

Like other influenza vaccines AGRIFLU® 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.

AGRIFLU® follows the World Health Organisation (WHO) and National Advisory Committee on Immunization (NACI) recommendation for vaccination for the northern hemisphere for the 2017/2018 season.

When it should not be used:

AGRIFLU® 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 (2017/2018 season)

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

A/Michigan/45/2015 (H1N1)pdm09-like virus (A/Singapore/GP1908/2015 IVR-180 (H1N1));
15 micrograms HA[§]

A/Hong Kong/4801/2014 (H3N2)-like virus (A/Hong Kong/4801/2014 NYMC X-263B (H3N2));
15 micrograms HA[§]

B/Brisbane/60/2008-like virus (B/Brisbane/60/2008);
15 micrograms HA[§]

Per 0.5 ml dose

[§] haemagglutinin

This vaccine complies with the WHO recommendations (northern hemisphere) for the 2017/2018 season.

What the important nonmedicinal ingredients are:

Sodium chloride, Potassium chloride, Potassium dihydrogen phosphate, Disodium phosphate dihydrate, Magnesium chloride hexahydrate, Calcium chloride dihydrate, Water for Injection, Thimerosal (multi-dose vial only).

May also contain trace amounts of:

Neomycin, kanamycin, egg proteins, ovalbumin (residual), Formaldehyde, polysorbate 80, cetyltrimethylammonium bromide (CTAB), barium (residual), or citrates (residual).

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

What dosage forms it comes in:

Pre-filled Syringe:
Sterile suspension for intramuscular injection in pre-filled syringe provided as packages containing one or ten single dose pre-filled glass syringes (Type I), without needles. The syringe may be

fitted alternatively with a Luer Lock system.

AGRIFLU® pre-filled syringes do not contain thimerosal or any other preservative.

Multi-dose vial:
Provided as packages containing one or ten multi-dose Type I glass vials closed with a Type I, grey, siliconized, bromobutyl stopper.

AGRIFLU® multi-dose vials contain thimerosal as a preservative.

The syringe plunger and vial stopper do not contain latex and AGRIFLU® is considered safe for use in persons with latex allergies.

WARNINGS AND PRECAUTIONS

AGRIFLU® 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.

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

If Guillain Barré-Syndrome (GBS) has occurred within six weeks of previous influenza vaccination, the decision to give AGRIFLU® should be based on careful consideration of the potential benefits and risks.

Immunocompromised patients may have a diminished immune response to AGRIFLU®. It is possible that antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.

BEFORE you use AGRIFLU®, 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)

AGRIFLU® 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 AGRIFLU® may not protect 100% of individuals against influenza disease.

INTERACTIONS WITH THIS MEDICATION

Overview

No interaction between AGRIFLU® and other vaccines or medication is 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.

PROPER USE OF THIS MEDICATION

Usual dose:

Age Group	Dose	No. of Doses
6 to 35 months	0.25 mL or 0.5 mL	1 or 2
3 to 8 years	0.5 mL	1 or 2
>9 years	0.5 mL	1

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.

NACI recommends that children 6 to 35 months of age should be given a full dose (0.5 mL) of trivalent inactivated influenza vaccine (TIV) instead of the previously recommended half dose (0.25 mL). This NACI recommendation applies whether the child is being given one dose of TIV or a two dose series.

Immunization should be carried out by intramuscular injection.

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.

Missed Dose: If a child's second dose is missed, it can be given at any time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Vaccination with AGRIFLU® (influenza vaccine, surface antigen, inactivated) cannot cause influenza because the vaccine does not contain live virus.

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, injection-site cellulitis-like reactions (some cases of swelling, pain, and redness extending more than 10 cm and lasting more than 1 week), and extensive swelling of injected limb lasting more than one week have been reported.

The most common (≥ 10%) local (injection-site) adverse reactions observed in clinical studies were injection site pain, induration, 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 AGRIFLU®*, contact your doctor or pharmacist.*

HOW TO STORE IT

AGRIFLU® should be stored at 2°C to 8°C (in a refrigerator), not frozen. The syringe and vial should be kept in the outer carton, thus protecting it from light. The multi-dose vial must be used within 28 days from the initial removal of the first dose (first needle puncture into vial) and between uses, return the multi-dose vial to the recommended storage conditions. The number of needle punctures should not exceed 10 per multi-dose vial.

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

The product has a shelf life of 1 year.

Do not use 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.seqirus.ca

or by contacting Seqirus at 1-855-358-8966

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