

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AGRIFLU (Influenza Virus Vaccine) safely and effectively. See full prescribing information.

AGRIFLU, Influenza Virus Vaccine

Suspension for intramuscular injection

2013-2014 Formula

Initial U.S. Approval: 2009

RECENT MAJOR CHANGES

DOSAGE AND ADMINISTRATION (2) 10/2013

INDICATIONS AND USAGE

AGRIFLU is a vaccine indicated for the active immunization for the prevention of disease caused by influenza virus subtypes A and type B contained in the vaccine. (1)

AGRIFLU is approved for use in persons 18 years of age and older.

DOSAGE AND ADMINISTRATION

A single 0.5mL dose for intramuscular injection. (2.2)

DOSAGE FORMS AND STRENGTHS

AGRIFLU, a sterile suspension for injection, is supplied in two presentations:

- 0.5 mL single-dose pre-filled syringes. (3,11)
- 5.0 mL multi-dose vial containing 10 doses (each dose is 0.5 mL) (3,11)

CONTRAINDICATIONS

Hypersensitivity to egg proteins, kanamycin and neomycin or other components of the vaccine, or life-threatening reaction to previous influenza vaccination. (4.1, 11)

FULL PRESCRIBING INFORMATION: CONTENTS*

1. INDICATIONS AND USAGE
2. DOSAGE AND ADMINISTRATION
 - 2.1 Preparation for Administration
 - 2.2 Recommended Dose and Schedule
3. DOSAGE FORMS AND STRENGTHS
4. CONTRAINDICATIONS
 - 4.1 Hypersensitivity
5. WARNINGS AND PRECAUTIONS
 - 5.1 Guillain-Barré Syndrome
 - 5.2 Altered Immunocompetence
 - 5.3 Preventing and Managing Allergic Reactions
 - 5.4 Limitations of Vaccine Effectiveness
6. ADVERSE REACTIONS
 - 6.1 Overall Adverse Reactions
 - 6.2 Clinical Trials Experience
 - 6.3 Postmarketing Experience
7. DRUG INTERACTIONS
 - 7.1 Concomitant Use With Other Vaccines
 - 7.2 Concurrent Use With Immunosuppressive Therapies

WARNINGS AND PRECAUTIONS

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. (5.1)

Immunocompromised patients may have a diminished immune response to AGRIFLU. (5.2)

The tip caps of the AGRIFLU prefilled syringes may contain natural rubber latex which may cause allergic reactions in latex sensitive individuals. (5.3)

ADVERSE REACTIONS

The most common ($\geq 10\%$) local (injection-site) adverse reactions was injection site pain. (6)

The most common ($\geq 10\%$) systemic adverse reactions were headache, myalgia, and malaise. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Vaccines at 1-877-683-4732 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

DRUG INTERACTIONS

Do not mix with any other vaccine in the same syringe. (7.1)

USE IN SPECIFIC POPULATIONS

Safety and effectiveness of AGRIFLU has not been established in pregnant women, nursing mothers, and children. (8.1, 8.3)

Antibody responses were lower in the geriatric population than in younger subjects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION

Issued: 10/2013, Rev.6

8. USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

11. DESCRIPTION

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14. CLINICAL STUDIES

15. REFERENCES

16. HOW SUPPLIED/STORAGE AND HANDLING

- 16.1 How Supplied
- 16.2 Storage and Handling

17. PATIENT COUNSELING INFORMATION

17.1 Information for Patients

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

AGRIFLU[®] is a vaccine indicated for the active immunization for the prevention of disease caused by influenza virus subtypes A and type B contained in the vaccine.

AGRIFLU is approved for use in persons 18 years of age and older. (*see CLINICAL STUDIES, [14]*)

2. DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

Shake each pre-filled syringe to aid inspection before administering the vaccine and shake the multi-dose vial each time before withdrawing a dose of vaccine. Inspect AGRIFLU visually for the presence of particulate matter or discoloration prior to administration, whenever suspension and container permit. If either of these conditions exists, do not use the contents. (*see DESCRIPTION [11]*)

Between uses, return the multi-dose vial to the recommended storage conditions between 2° and 8°C (36° and 46°F). 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.

Do not use the vaccine if it has been frozen. Needles should be disposed of properly and not recapped.

2.2 Recommended Dose and Schedule

AGRIFLU 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.

3. DOSAGE FORMS AND STRENGTHS

AGRIFLU is a sterile clear aqueous suspension for intramuscular injection that is supplied in two presentations:

- 0.5 mL single-dose pre-filled syringes with no preservative.
- 5.0 mL multi-dose vial containing 10 doses (each dose is 0.5 mL)

(*See DESCRIPTION [11] for a listing of vaccine components.*)

4. CONTRAINDICATIONS

4.1 Hypersensitivity

Do not administer AGRIFLU to anyone with known systemic hypersensitivity reactions to egg proteins (eggs or egg products), kanamycin and neomycin, or any other constituent of the vaccine (*see DESCRIPTION [11]*), or to anyone who has had a life-threatening reaction to previous influenza vaccination.

5. WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

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.

5.2 Altered Immunocompetence

The immune response to AGRIFLU in immunocompromised persons, including individuals receiving immunosuppressive therapy, may be lower than in immunocompetent individuals.

5.3 Preventing and Managing Allergic Reactions

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

The tip caps of the AGRIFLU prefilled syringes may contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

5.4 Limitations of Vaccine Effectiveness

Vaccination with AGRIFLU may not protect all recipients.

6. ADVERSE REACTIONS

6.1 Overall Adverse Reactions

The most common local (injection site) adverse reactions observed in clinical studies with AGRIFLU were pain, induration, swelling, and erythema. The most common systemic adverse reactions observed were headache, myalgia, and malaise. These reactions are typically mild. Serious allergic reactions, including anaphylactic shock, have been observed during postmarketing surveillance in individuals receiving AGRIFLU.

6.2 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine, and may not reflect rates observed in clinical practice. The most common local adverse reactions and general adverse reactions observed with AGRIFLU were pain and erythema at the injection site, headache, myalgia, and malaise.

Clinical safety data have been obtained from three randomized, controlled trials one of which was a placebo controlled efficacy study.^{1,2,3} In these trials, 13480 subjects were randomized to receive either AGRIFLU (5338 subjects included in the safety analysis), a U.S.-licensed comparator influenza vaccine (435 included in the safety analysis), an investigational inactivated influenza vaccine (3813 included in the safety analysis), or placebo (3894 included in the safety analysis). (*see CLINICAL STUDIES [14]*). The overall enrolled population from the 3 studies was 18-64 years of age (mean 33 years), 57 % were female and 75% were Caucasian, 6% were Black, 18% were Hispanic and 1% were of other ethnic origin. The percentage of subjects who had a record of receiving a previous influenza vaccination was 13%. (*see CLINICAL STUDIES [14]*). In all three studies, solicited local (injection site) and systemic reactions were collected from subjects who completed a symptom diary card for seven days following vaccination. Safety data are presented in Table 1.

Table 1: Percentage of Subjects Reporting Solicited Adverse Reactions in Days 1-7 After Vaccination With AGRIFLU or Comparators

	Percentage of Subjects with Adverse Reactions					
	Study 1 ¹ 2007 NCT00464672 (18-64 years)		Study 2 ² 2007-2008 NCT00617851 (18-49 years)		Study 3 ³ 2007-2008 NCT 00630331 (18-49 years)	
	AGRIFLU N=460	Comparator ^a N=233	AGRIFLU N=1209	Comparator ^a N=202	AGRIFLU N=3669	Placebo N=3895
Local Adverse Reactions						
Injection site pain						
Any pain	25	30	22	22	24	10
Severe pain ^b	<1	0	<1	<1	<1	<1
Induration	2	1	1	1	6	3
Swelling	<1	1	1	<1	5	3
Erythema	<1	1	<1	<1	13	10
Ecchymosis	<1	0	<1	<1	3	4
Systemic Adverse Reactions						
Headache	23	18	24	24	15	15
Myalgia	14	16	18	20	10	7
Malaise	12	12	12	12	7	6
Fatigue	10	10	9	8	11	10
Chills	5	7	7	8	6	6
Arthralgia	7	6	6	7	3	3
Sweating	5	5	4	4	3	3
Fever ($\geq 38^{\circ}\text{C}$)	2	3	4	3	<1	<1

^aComparator is U.S.-licensed trivalent, inactivated influenza virus vaccine (Fluvirin).

^bSevere injection site pain= local reaction leading to the inability to perform normal daily activities.

In the two studies with a U.S.-licensed influenza comparator vaccine, unsolicited adverse events were reported by subjects over a 3-week period after vaccination. Unsolicited adverse events that occurred in > 1% of subjects included influenza-like illness (4% of AGRIFLU subjects and 3% of active comparator subjects) and headache (2% of AGRIFLU and comparator subjects). A total of 17% of subjects in both the AGRIFLU and the comparator groups reported unsolicited adverse events: 15% and 16% of subjects in the AGRIFLU and in the comparator groups, respectively, had mild unsolicited adverse events, 2% and 1% of subjects had moderate adverse events, and <1 % of subjects in both groups had severe adverse events.

In the placebo controlled efficacy study, all unsolicited adverse events were collected for 7 days after vaccination and selected adverse events (serious adverse events, onset of chronic illness, AEs that necessitated a physician consultation and/or led to withdrawal from the study) for up to 3 weeks after vaccination. A total of 13% and 14% of subjects in the AGRIFLU and the comparator groups reported unsolicited adverse events: in both the AGRIFLU and in the comparator groups, 7% of subjects had mild unsolicited adverse events, 5% of subjects had

moderate adverse events, and 2% of subjects had severe adverse events. Unsolicited adverse events reported in the 3 week period that occurred in > 1% of subjects included pharyngolaryngeal pain (2% of both AGRIFLU and placebo subjects).

6.3 Postmarketing Experience

The following additional adverse events have been identified during postapproval use of AGRIFLU in Europe since 2003. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

Blood and lymphatic system disorders:

Thrombocytopenia (some very rare cases were severe with platelet counts less than 5,000 per mm³).

Eye disorders:

Conjunctivitis, eyelid edema, eye redness

Gastrointestinal disorders:

Diarrhea, nausea, vomiting, abdominal pain

General disorders and administration site conditions:

Local injection site reactions, including pain, pain limiting limb movement, redness, swelling, warmth, ecchymosis, induration, local lymphadenopathy, Injection-site cellulitis-like reaction (some cases of swelling, pain, and redness extending more than 10 cm and lasting more than one week), Extensive swelling of injected limb lasting more than one week, and general disorders including, chills, fever, malaise, fatigue, asthenia, facial edema.

Immune system disorders:

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

Musculoskeletal and connective tissue disorders:

Arthralgia, myalgia.

Nervous system disorders:

Headache, 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

Skin and Subcutaneous disorders:

Pruritus, urticaria and non-specific rash

Vascular disorders:

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

6.4 Adverse events associated with influenza vaccines

Anaphylaxis has been reported after administration of AGRIFLU. AGRIFLU contains egg proteins, which can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Allergic reactions include hives, angioedema, allergic asthma, and systemic anaphylaxis [see CONTRAINDICATIONS (4) and DESCRIPTION (11)].

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with subsequent vaccines prepared

from other influenza viruses is unclear. If influenza vaccine does pose a risk, it is probably slightly more than 1 additional case/1 million persons vaccinated.

Neurological disorders temporally associated with influenza vaccination such as encephalopathy, optic neuritis/neuropathy, partial facial paralysis, and brachial plexus neuropathy have been reported.

Microscopic polyangitis (vasculitis) has been reported temporally associated with influenza vaccination.

7. DRUG INTERACTIONS

7.1 Concomitant Use With Other Vaccines

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

AGRIFLU should not be mixed with any other vaccine in the same syringe.

7.2 Concurrent Use With Immunosuppressive Therapies

Immunosuppressive therapies including corticosteroids may reduce the immune response to AGRIFLU.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B.

Reproduction studies have been performed in female rabbits at a dose approximately 15 times the human dose (on a mg/kg basis) and have revealed no evidence of impaired fertility or harm to the fetus due to AGRIFLU. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, AGRIFLU should be given to a pregnant woman only if clearly needed.

In two reproduction toxicity studies, the effect of AGRIFLU on embryo-fetal or post-natal development was evaluated in pregnant rabbits. Animals were administered AGRIFLU 3 times prior to gestation, during the period of organogenesis (gestation day 7) and later in pregnancy (gestation day 20), 0.5 mL/rabbit/occasion (approximately 15-fold excess relative to the projected human dose on a body weight basis) by intramuscular injection. Effects on post-natal development could not be fully evaluated, however, there were no adverse effects attributable to the vaccine on mating, female fertility, pregnancy, or embryo-fetal development. There were no vaccine related fetal malformations or other evidence of teratogenesis noted in this study.

8.3 Nursing Mothers

AGRIFLU has not been evaluated in nursing mothers. It is not known whether AGRIFLU is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when AGRIFLU is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

8.5 Geriatric Use

In eight clinical studies, 1221 subjects 65 years of age and older received AGRIFLU. Antibody responses in geriatric subjects were lower after administration of AGRIFLU in comparison to younger adult subjects. Adverse event rates were generally similar in frequency in geriatric

subjects (≥ 65 years of age) to those reported in younger adults, although some differences were observed.

11. DESCRIPTION

AGRIFLU, Influenza Virus Vaccine, for intramuscular injection is a trivalent inactivated influenza virus vaccine prepared from virus propagated in the allantoic cavity of embryonated hens' eggs inoculated with an 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 vaccine preparation by subsequent purification steps.

AGRIFLU is a sterile clear aqueous suspension and is formulated to contain a total of 45 micrograms (mcg) hemagglutinin (HA) per 0.5-mL dose in the recommended ratio of 15 mcg HA of each of the following three influenza virus strains recommended for the 2013/2014 influenza season: A/California/7/2009, NYMC X-181 (H1N1); A/Texas/50/2012, NYMC X-223 (H3N2); and B/Massachusetts/2/2012.

The 0.5 mL pre-filled syringe presentation is manufactured and formulated without thimerosal or any other preservative.

The 5.0 mL multi-dose vial presentation contains thimerosal, a mercury derivative, added as a preservative. Each 0.5 mL dose from the multi-dose vial contains 25 mcg mercury.

Each 0.5 mL dose from the pre-filled syringe or multi-dose vial may contain residual amounts of egg proteins (< 0.4 mcg), formaldehyde (≤ 10 mcg), polysorbate 80 (≤ 50 mcg), and CTAB (≤ 12 mcg). Each dose may also contain residual amounts of neomycin (≤ 0.02 mcg by calculation), kanamycin (≤ 0.03 mcg by calculation), and barium (< 0.5 mcg by calculation), which are used during the initial stages of manufacture. The tip caps of the syringes may contain natural rubber latex. The syringe plunger and the multi-dose vial do not contain natural rubber latex.

12. CLINICAL PHARMACOLOGY

12.1 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 subjects⁴.

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 the United States in the upcoming winter.

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 year⁵.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14. CLINICAL STUDIES

14.1 Efficacy against culture-confirmed influenza

A multinational (U.S., Finland, and Poland), randomized, observer-blind, placebo controlled trial (Study 3³) was performed to assess clinical efficacy and safety of AGRIFLU in the 2007-2008 influenza season in adults aged 18 to 49 years. A total of 11404 subjects were enrolled to receive in a 1:1:1 ratio AGRIFLU (N=3676), an investigational inactivated influenza vaccine (N=3828) or placebo (N=3900). Among the overall study population enrolled, the mean age was 33 years, 55% were women; 84% were Caucasian, 7% were Hispanic, 7% were Black, and 2% were of other ethnic origin.

AGRIFLU efficacy was assessed by the prevention of culture-confirmed symptomatic influenza illness caused by vaccine-like virus strains compared to placebo. Influenza cases were identified by active and passive surveillance of influenza-like illness (ILI). ILI was defined according to Centers for Disease Control and Prevention (CDC) case definition, i.e., a fever (oral temperature $\geq 100.0^{\circ}\text{F}$ / 38°C) and cough or sore throat. After an episode of ILI, nose and throat swab samples were collected for analysis. Vaccine efficacy against vaccine-matched influenza strains, against all influenza strains, and against individual influenza subtypes was calculated (Tables 2 and 3).

Table 2: Vaccine Efficacy against Culture-Confirmed Influenza (Study 3, NCT00630331)¹

			Attack Rate	Vaccine Efficacy ²	
	N ³	n ⁴	%	%	LL ⁵ 97.5% CI
Antigenically Matched Strains					
AGRIFLU	3638	9	0.25	78.4	52.1
Placebo	3843	44	1.14	--	--
All Culture-Confirmed Influenza					
AGRIFLU	3638	49	1.35	63.0	46.7
Placebo	3843	140	3.64	--	--

¹Study 3 was conducted during the 2007/2008 influenza season; ²Simultaneous one-sided 97.5% confidence intervals for the vaccine efficacy of each influenza vaccine relative to placebo based on the Sidak-corrected score confidence intervals for the two relative risks. Vaccine Efficacy = (1 - Relative Risk) x 100 %; ³N = number of subjects in the per protocol efficacy population; ⁴n = number of subjects with Influenza; ⁵LL = lower limit of one-sided 97.5% CI

Table 3: Comparative Efficacy of AGRIFLU versus Placebo Against Culture-Confirmed Influenza by Influenza Subtype (Study 3, NCT00630331)¹

	AGRIFLU (N=3638)		Placebo (N=3843)		Vaccine Efficacy ²	
	Attack Rate	Number of Subjects with Influenza	Attack Rate	Number of Subjects with Influenza	%	Lower Limit of One-Sided 97.5% CI
Antigenically Matched Strains						
A/H3N2 ³	0.03%	1	0	0	--	--
A/H1N1	0.22%	8	1.12%	43	80.3	54.7
B ³	0	0	0.03%	1	--	--
All Culture-Confirmed Influenza						
A/H3N2	0.33%	12	0.65%	25	49.3	-9.0
A/H1N1	0.27%	10	1.48%	57	81.5	60.9
B	0.74%	27	1.59%	61	53.2	22.2

¹Study 3 was conducted during the 2007/2008 influenza season; ²Simultaneous one-sided 97.5% confidence intervals for the vaccine efficacy of each influenza vaccine relative to placebo based on the Sidak-corrected score confidence intervals for the two relative risks. Vaccine Efficacy = (1 - Relative Risk) x 100 %; ³There were too few cases of influenza due to vaccine-matched influenza H3N2 or B to adequately assess vaccine efficacy.

14.2 Immunological Evaluation

In the three randomized, controlled clinical trials with AGRIFLU, immune responses, specifically hemagglutination inhibition (HI) antibody titers to each virus strain in the vaccine, were evaluated in sera obtained 21 days after administration of AGRIFLU. These studies included Study 3, in which immunogenicity was evaluated in a subset of subjects, comprised of the first 1045 subjects enrolled and randomized at the US sites.

In the first clinical trial (Study 1¹), performed in Argentina, 643 adult subjects (424 and 219 for AGRIFLU and U.S.-licensed comparator influenza vaccine, respectively) were enrolled and evaluable. Among the overall study population enrolled, 61% were women, and the distribution of subjects by ethnicity was 79% Caucasian, 20% Hispanic, and 1% Asian; the subjects' age ranged between 18 and 64 years (mean age of 38.5 years).

In the second clinical trial (Study 2²), performed in the Dominican Republic, subjects were randomly assigned at a 2:2:2:1 ratio to receive either one of three consecutive AGRIFLU lots or the U.S.-licensed influenza vaccine used for comparison of the safety profile. A total of 1376 adult subjects 18 to 49 years of age were enrolled and evaluable (1182 and 194 for AGRIFLU and comparator influenza vaccine, respectively). Among the overall study population enrolled, 70% were women; 97% were Hispanic, 2% were Black, and 1% were of other ethnic origin; subjects' age ranged between 18 and 49 years (mean of 31 years). For all three studies, the following immunogenicity endpoints were assessed: 1) the lower bounds of the 2-sided 95% confidence intervals (CI) for the proportion of subjects with HI antibody titers of 1:40 or greater after vaccination, should exceed 70% for each vaccine antigen strain; and 2) the lower bounds of the 2-sided 95% CI for rates of seroconversion (defined as \geq 4-fold increase in post-vaccination

HI antibody titers from pre-vaccination titers of $\geq 1:10$ or an increase in titers from $< 1:10$ to $\geq 1:40$), should exceed 40% for each vaccine antigen strain. In both studies with a U.S.-licensed influenza vaccine comparator the active comparator arm was used for comparison of safety only.

Table 4: Serum HI Antibody Responses in Adults 21 Days After Vaccination With AGRIFLU

	Vaccine Strain	% HI Titer $\geq 1:40$ (95% CI)	% Seroconversion ^b (95% CI)
Study 1 2007 (18-64 years) NCT00464672 N=424	A/H1N1	93 (90-95)	74 (69-78)
	A/H3N2	96 (94-98)	72 (68-76)
	B	91 (87-93)	77 (72-81)
Study 2 2007-2008 (18-49 years) NCT00617851 N=1182 ^a	A/H1N1	98 (97-99)	94 (93-95)
	A/H3N2	99 (98-100)	67 (65-70)
	B	87 (85-89)	84 (82-86)
Study 3 2007-2008 (18-49 years) NCT00630331 N=695	A/H1N1	98 (97-99)	75 (71-78)
	A/H3N2	99 (98-100)	68 (64-71)
	B	92 (90-94)	68 (65-72)

^apooled number of subjects receiving one of the three manufacturing lots of AGRIFLU.

^bRates of seroconversion = percentage of subjects with either a pre-vaccination HI titer $< 1:10$ and a post-vaccination HI titer $> 1:40$ or a pre-vaccination HI titer $> 1:10$ and at least a four-fold rise in post-vaccination HI antibody titer.

15. REFERENCES

- 1 NCT00464672; see www.clinicaltrials.gov
- 2 NCT00617851; see www.clinicaltrials.gov
- 3 NCT00630331; see www.clinicaltrials.gov
- 4 Hobson D, Curry RL, Beare A, et. al. The role of serum hemagglutinin-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. J Hyg Camb 1972; 767-777.
- 5 Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and Mortality Weekly Reports 2011; 60(33):1128-1132. Centers for Disease Control and Prevention, Atlanta, GA.

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

AGRIFLU product presentations are listed in Table 5 below:

Table 5: AGRIFLU Product Presentations

Presentation	Carton NDC Number	Components
Pre-filled syringe	46028-112-01	Ten 0.5 mL single-dose pre-filled syringes without needles (tip cap may contain latex; plunger contains no latex) [NDC 46028-112-11]
Multi-dose vial	46028-112-02	One 5.0 mL multi-dose vial, containing ten 0.5 mL doses (contains no latex) [NDC 46028-112-12]

16.2 Storage and Handling

Store refrigerated at +2°C to +8°C (36°F to 46°F).

Do not freeze. Discard if the vaccine has been frozen.

Protect from light.

Do not use after the expiration date.

Between uses, return the multi-dose vial to the recommended storage conditions.

17. PATIENT COUNSELING INFORMATION

17.1 Information for Patients

Provide the following information or instructions to vaccine recipients:

Inform on potential benefits and risks of immunization with AGRIFLU.

Explain that (1) AGRIFLU contains non-infectious particles and cannot cause influenza and (2) AGRIFLU is intended to provide protection against illness due to influenza viruses only, and cannot provide protection against other respiratory illnesses.

Instruct to report any severe or unusual adverse reactions to their healthcare provider.

Instruct that annual vaccination is recommended.

AGRIFLU is a registered trademark of Novartis Vaccines and Diagnostics, Inc.

Manufactured by: Novartis Vaccines and Diagnostics S.r.l., Siena, Italy

An affiliate of: Novartis Vaccines and Diagnostics, Inc., 350 Massachusetts Avenue,
Cambridge, MA USA 02139

1-877-683-4732