

**NURSE PROTOCOL FOR  
PREVENTION OF  
INFLUENZA A (H1N1) VIRUS INFECTION  
USING INFLUENZA A (H1N1) 2009 MONOVALENT VACCINE LIVE, INTRANASAL  
AND  
INFLUENZA A (H1N1) 2009 MONOVALENT VACCINE, INJECTION**

**DEFINITION**            The novel H1N1 Influenza virus is a very unusual virus. This particular genetic combination of influenza segments has not been recognized before in the United States or elsewhere.

**ETIOLOGY**            The hallmark of influenza viruses is their ability to undergo constant and dramatic change. Many different animals and humans get infected with influenza viruses, but the viruses generally stick with one species or another. However, sometimes influenza viruses jump from one species to another, and sometimes, viruses from different species can infect the same host and result in a new combination of virus genes. This last scenario is what happened and resulted in the novel H1N1 influenza virus.

**SUBJECTIVE/  
OBJECTIVE**            The patient is asymptomatic and does not present any signs of illness. The patient denies any allergies or hypersensitivity to eggs or egg proteins, or life threatening reactions to previous influenza vaccination.

**ASSESSMENT**            The patient meets criteria for receiving the novel H1N1 influenza vaccination.

**PLAN**                    **THERAPEUTIC**

**Note:** Refer to the description section of each vaccine for specific components relating to allergies and hypersensitivity.

**MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal**

MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is indicated for the active immunization of individuals 2-49 years of age against influenza disease caused by pandemic (H1N1) 2009 virus.

See Table 1 for dosage schedule by age group.

**Table 1.  
Dosage by Age Group**

<b>AGE GROUP</b>	<b>DOSAGE SCHEDULE</b>
Children 2 years through 9 years	2 doses (0.2 mL* each, approximately 1 month apart)
Children, adolescents and adults age 10 through 49 years	1 dose (0.2 mL*)

\*NOTE: Each 0.2 mL dose is administered as 0.1 mL per nostril.

### **Administrative Instructions**

Each sprayer contains a single dose; approximately one-half of the contents should be administered into each nostril. Refer to the package insert for step-by-step administration instructions. Once the vaccine has been administered, the sprayer should be disposed of according to the standard procedures for medical waste (e.g., sharps container or biohazard container).

### **Dosage Forms and Strengths**

Pre-filled, single-dose intranasal sprayer containing 0.2 mL suspension.

## **CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS**

### **Hypersensitivity**

MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is contraindicated in individuals with a history of hypersensitivity, especially anaphylactic reactions, to eggs, egg proteins, gentamicin, gelatin, or arginine or with life-threatening reactions to previous influenza vaccinations.

### **Concomitant Pediatric and Adolescent Aspirin Therapy and Reye's Syndrome**

MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is contraindicated in children and adolescents (2-17 years of age) receiving aspirin therapy or aspirin-containing therapy, because of the association of Reye's syndrome with aspirin and wild-type influenza infection.

### **Risks in Children Less Than 24 Months of Age**

Do not administer MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist to children less than 24 months of age. In clinical trials, an increased risk of wheezing post-vaccination was observed in FluMist recipients less than 24 months of age. An increase in hospitalizations was observed in children less than 24 months of age after vaccination with FluMist.

### **Asthma/Recurrent Wheezing**

MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist should not be administered to any individuals with asthma or children less than 5 years of age with recurrent wheezing because of the potential for increased risk of wheezing post vaccination unless the potential benefit outweighs the potential risk.

Do not administer MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist to individuals with severe asthma or active wheezing because these individuals have not been studied in clinical trials.

### **Guillain-Barre' Syndrome**

If Guillain-Barre' syndrome has occurred within 6 weeks of any prior influenza vaccination, the decision to give MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist should be based on careful consideration of the potential benefits and potential risks. See also Adverse Reactions.

### **Altered Immunocompetence**

Administration of MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal, or FluMist live virus vaccine, to immunocompromised persons should be based on careful consideration of potential benefits and risks. Although FluMist was studied in 57 asymptomatic or mildly symptomatic adults with HIV infection (see manufacturer's information on Clinical Studies), data supporting the safety and effectiveness of FluMist administration in immunocompromised individuals are limited.

### **Medical Conditions Predisposing to Influenza Complications**

The safety of MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist in individuals with underlying medical conditions that may predispose them to complications following wild-type influenza infection has not been established. Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal should not be administered unless the potential benefit outweighs the potential risk.

### **Management of Acute Allergic Reactions**

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

### **Limitations of Vaccine Effectiveness**

MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal may not protect all individuals receiving the vaccine.

## **ADVERSE REACTIONS**

**MedImmune's** Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal and seasonal trivalent Influenza Vaccine Live, Intranasal (FluMist) are manufactured by the same process.

The data in this section were obtained from clinical trials and post-marketing experience with FluMist.

See product package insert for a complete list of adverse reactions.

- Abdominal pain/nausea, vomiting, diarrhea
- Runny nose/congestion/sinusitis
- Sneezing
- Headache
- Cough

- Fever/chills
- Sore throat
- Muscle aches
- Decreased appetite
- Irritability
- Guillain-Barré Syndrome
- Bell's Palsy
- Rash
- Epistaxis
- Mitochondrial encephalomyopathy (Leigh Syndrome)

Hypersensitivity, including anaphylactic reaction, has been reported during post-marketing experience with FluMist.

## **DRUG INTERACTIONS**

MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal and seasonal trivalent Influenza Vaccine Live, Intranasal (FluMist) are manufactured by the same process.

### **Aspirin Therapy**

Do not administer MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist to children or adolescents who are receiving aspirin therapy or aspirin-containing therapy.

### **Antiviral Agents Against Influenza A and/or B**

The concurrent use of MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist with antiviral agents that are active against influenza A and/or B viruses has not been evaluated. However, based upon the potential for antiviral agents to reduce the effectiveness of MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal, do not administer this vaccine until 48 hours after the cessation of antiviral therapy and antiviral agents should not be administered until two weeks after administration of this vaccine unless medically indicated. If antiviral agents and MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist are administered concomitantly, revaccination should be considered when appropriate.

### **Concomitant Inactivated Vaccines**

There are no data on the concomitant administration of MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal and seasonal trivalent Influenza Virus Vaccines.

The safety and immunogenicity of MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist when administered concurrently with inactivated vaccines have not been determined. Studies of FluMist excluded subjects who received any inactivated or subunit vaccine within two weeks of enrollment. Therefore, healthcare providers should consider the risks and benefits of concurrent administration of MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal with inactivated vaccines.

### **Concomitant Live Vaccines**

There are no data on the concomitant administration of MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal and FluMist.

Concurrent administration of FluMist with the measles, mumps and rubella vaccine and the varicella vaccine was studied in 1245 children 12-15 months of age. Adverse events were similar to those seen in other clinical trials with FluMist (see Adverse Reactions). No evidence of interference with immune responses to measles, mumps, rubella, varicella and FluMist vaccines was observed. Concurrent administration of FluMist with the measles, mumps and rubella vaccine and the varicella vaccine in children >15 months of age has not been studied.

### **Intranasal Products**

There are no data regarding co-administration of MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist with other intranasal preparations.

## **USE IN SPECIFIC POPULATIONS**

MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal and seasonal trivalent Influenza Vaccine Live, Intranasal (FluMist) are manufactured by the same process.

### **Pregnancy**

#### ***Pregnancy Category C***

Animal reproduction studies have not been conducted with MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist. It is not known whether MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist should be given to a pregnant woman only if clearly needed.

The effect of FluMist on embryo-fetal and pre-weaning development was evaluated in a developmental toxicity study using pregnant rats receiving the frozen formulation. Groups of animals were administered FluMist either once (during the period of organogenesis on gestation day 6) or twice (prior to gestation and during the period of organogenesis on gestation day 6), 250 microliter/rat/occasion (approximately 110-140 human dose equivalents), by intranasal instillation. No adverse effects on pregnancy, parturition, lactation, embryo-fetal or pre-weaning development were observed. There were no FluMist related fetal malformations or other evidence of teratogenesis noted in this study.

### **Nursing Mothers**

It is not known whether MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist is excreted in human milk. Therefore, as some viruses are excreted in human milk and additionally, because of the possibility of shedding of vaccine virus and the close proximity of a nursing infant and mother, caution should be exercised if MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist is administered to nursing mothers.

### **Pediatric Use**

Safety and effectiveness of FluMist has been demonstrated for children 2 years of age and older with reduction in culture-confirmed influenza rates compared to active control (injectable

influenza vaccine made by Sanofi Pasteur Inc.) and placebo (see Clinical Studies). Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is not approved for use in children <24 months of age. FluMist use in children <24 months has been associated with increased risk of hospitalization and wheezing in clinical trials (see manufacturer's information on Warnings and Precautions and Adverse Reactions).

### **Geriatric Use**

MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is not approved for use in individuals  $\geq 65$  years of age. Subjects with underlying high-risk medical conditions (n=200) were studied for safety. Compared to controls, FluMist recipients had a higher rate of sore throat.

### **Use in Individuals 50-64 Years of Age**

MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is not approved for use in individuals 50-64 years of age. In Study AV009, effectiveness of FluMist was not demonstrated in individuals 50-64 years of age (n=641). Solicited adverse events were similar in type and frequency to those reported in younger adults.

## **DESCRIPTION**

MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is a live monovalent vaccine for administration by intranasal spray. The influenza virus strain in Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is (a) cold-adapted (ca) (i.e., it replicates efficiently at 25°C, a temperature that is restrictive for replication of many wild-type influenza viruses); (b) temperature-sensitive (ts) (i.e., it is restricted in replication at 39°C, a temperature at which many wild-type influenza viruses grow efficiently); and (c) attenuated (att) (it does not produce classic influenza-like illness in the ferret model of human influenza infection). The cumulative effect of the antigenic properties and the ca, ts, and att phenotypes is that the attenuated vaccine virus replicates in the nasopharynx to induce protective immunity.

No evidence of reversion has been observed in the recovered vaccine strains that have been tested (135 of possible 250 recovered isolates) using FluMist (see manufacturer's information on Clinical Studies). For the reassortant virus in MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal, the six internal gene segments responsible for ca, ts, and att phenotypes are derived from a master donor virus (MDV), and the two segments that encode the two surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA), are derived from the corresponding antigenically relevant pandemic (H1N1) 2009 wild-type virus. Thus, the virus contained in MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal, maintains the replication characteristics and phenotypic properties of the MDV and expresses the HA and NA of the pandemic (H1N1) 2009 virus. For the MDV, at least five genetic loci in three different internal gene segments contribute to the ts and att phenotypes; five genetic loci in three gene segments control the ca property.

Specific pathogen-free (SPF) eggs are inoculated with the reassortant strain and incubated to allow vaccine virus replication. The allantoic fluid of these eggs is harvested, pooled and then clarified by filtration. The virus is concentrated by ultracentrifugation and diluted with stabilizing buffer to obtain the final sucrose and potassium phosphate concentrations. The

viral harvests are then sterile filtered to produce monovalent bulks. Each lot is tested for ca, ts, and att phenotypes and is also tested extensively by in vitro and in vivo methods to detect adventitious agents. Monovalent bulks are diluted as required to attain the desired potency with stabilizing buffers. The bulk vaccine is then filled directly into individual sprayers for nasal administration.

Each pre-filled refrigerated MedImmune Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal sprayer contains a single 0.2 mL dose. Each 0.2 mL dose contains 106.5-7.5 FFU of the live attenuated influenza virus reassortant of the pandemic (H1N1) 2009 virus: A/California/7/2009 (H1N1)v. Each 0.2 mL dose also contains 0.188 mg/dose monosodium glutamate, 2.00 mg/dose hydrolyzed porcine gelatin, 2.42 mg/dose arginine, 13.68 mg/dose sucrose, 2.26 mg/dose dibasic potassium phosphate, 0.96 mg/dose monobasic potassium phosphate, and <0.015 mcg/mL gentamicin sulfate. The vaccine contains no preservatives.

The tip attached to the sprayer is equipped with a nozzle that produces a fine mist that is primarily deposited in the nose and nasopharynx. Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is a colorless to pale yellow liquid and is clear to slightly cloudy.

## **CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

Immune mechanisms conferring protection against influenza following receipt of FluMist vaccine are not fully understood. Likewise, naturally acquired immunity to wild-type influenza has not been completely elucidated. Serum antibodies, mucosal antibodies and influenza-specific T cells may play a role in prevention and recovery from infection.

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. 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.

### **Pharmacokinetics Biodistribution**

A biodistribution study of intranasally administered radiolabeled placebo was conducted in 7 healthy adult volunteers. The mean percentage of the delivered doses detected were as follows: nasal cavity 89.7%, stomach 2.6%, brain 2.4%, and lung 0.4%. The clinical significance of these findings is unknown.

## **NONCLINICAL TOXICOLOGY**

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Neither MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal nor FluMist have been evaluated for carcinogenic or mutagenic potential or potential to impair fertility.

## **HOW SUPPLIED/STORAGE AND HANDLING**

MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is supplied for intranasal delivery in a package of 10 pre-filled, single-use sprayers (NDC 66019-200-10).

### **Storage and Handling**

Once MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal has been administered, the sprayer should be disposed of according to the standard procedures for medical waste (e.g., sharps container or biohazard container).

*MEDIMMUNE's INFLUENZA A (H1N1) 2009 MONOVALENT VACCINE LIVE, INTRANASAL SHOULD BE STORED IN A REFRIGERATOR BETWEEN 2-8°C (35-46°F) UPON RECEIPT AND UNTIL USE. THE PRODUCT MUST BE USED BEFORE THE EXPIRATION DATE ON THE SPRAYER LABEL.*

### ***DO NOT FREEZE.***

The cold chain (2 to 8°C) must be maintained when transporting Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal.

## **PATIENT COUNSELING INFORMATION**

Vaccine recipients or their parents/guardians should be informed by the health care provider of the potential benefits and risks of MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal, and should be advised that there are two influenza vaccine formulations for this influenza season, the monovalent vaccine against disease caused by pandemic (H1N1) 2009 virus and seasonal trivalent influenza vaccine. The 2009 H1N1 Vaccine Information Statement (VIS) should be provided to the patient or parent/guardian.

### **Asthma and Recurrent Wheezing**

Ask the vaccinee or their parent/guardian if the vaccinee has asthma. For children <5 years of age, also ask if the vaccinee has recurrent wheezing since this may be an asthma equivalent in this age group.

### **Vaccination with a Live Virus Vaccine**

Vaccine recipients or their parents/guardians should be informed by the health care provider that MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is an attenuated live virus vaccine and has the potential for transmission to immunocompromised household contacts.

### **Adverse Event Reporting**

The vaccine recipient or the parent/guardian accompanying the vaccine recipient should be told to report any suspected adverse events to the physician or clinic where the vaccine was administered.

## REFERENCES

1. CDC, "Serum Cross-Reactive Antibody Response to a Novel Influenza A (H1N1) Virus After Vaccination with Seasonal Influenza Vaccine," *MMWR*, 2009; 58(19): 521-524.
2. MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal Patient Product Information.

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### **Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine, Injection**

Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine is an inactivated influenza virus vaccine indicated for immunization of persons 4 years of age and older against influenza disease caused by pandemic (H1N1) 2009 virus. See Table 2 for dosage by age group.

<b>AGE GROUP</b>	<b>DOSAGE</b>
Children 4 through 9 years of age	Two 0.5mL doses by intramuscular injection approximately 1 month apart
Children 10 through 17	A single 0.5mL dose by intramuscular injection.
18 years of age and older	A single 0.5mL dose by intramuscular injection, preferably in the region of the deltoid muscle of the upper arm

#### **Administration Instructions**

Inspect Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine syringes and multidose vials visually for particulate matter and/or discoloration prior to administration. If either of these conditions exists, the vaccine should not be administered.

For children, the needle size may range from 7/8 to 1¼ inches, depending on the size of the child's deltoid muscle, and should be of sufficient length to penetrate the muscle tissue. The anterolateral thigh can be used, but the needle should be longer, usually 1 inch.

For adults, a needle of ≥1 inch is preferred because needles <1 inch might be of insufficient length to penetrate muscle tissue in certain adults.

The vaccine should not be injected in the gluteal region or areas where there may be a major nerve trunk.

Shake the syringe vigorously before administering the vaccine and shake the multidose vial preparation each time before withdrawing a dose of vaccine.

Between uses, return the multidose vial to the recommended storage conditions between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the vaccine has been frozen.

A separate syringe and needle or a sterile disposable unit should be used for each injection to prevent transmission of infectious agents from one person to another. Needles should be disposed of properly and not recapped.

**Note: It is recommended that small syringes (0.5-mL or 1-mL) should be used to minimize any product loss.**

## **DOSAGE FORMS AND STRENGTHS**

Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine is a sterile suspension for intramuscular injection (see DESCRIPTION for the complete list of ingredients).

Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine is available in two presentations:

1. Prefilled single dose syringe, 0.5-mL. Thimerosal, a mercury derivative used during manufacture, is removed by subsequent purification steps to a trace amount ( $\leq 1$  mcg mercury per 0.5-mL dose).
2. Multidose vial, 5-mL. Contains thimerosal, a mercury derivative, added as a preservative. Each 0.5-mL dose from the multidose vial contains 25 mcg mercury.

## **CONTRAINDICATIONS**

### **Hypersensitivity**

Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine should not be administered to anyone with known systemic hypersensitivity reactions to egg proteins (eggs or egg products), polymyxin, neomycin, betapropiolactone and nonylphenol ethoxylate or to any component of Influenza A (H1N1) 2009 Monovalent Vaccine, or who has had a life-threatening reaction to previous influenza vaccinations. See Description below.

## **WARNINGS AND PRECAUTIONS**

### **Guillain-Barré Syndrome**

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine should be based on careful consideration of the potential benefits and risks.

### **Altered Immunocompetence**

If Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine is administered to immunocompromised persons, including individuals receiving immunosuppressive therapy, the expected immune response may not be obtained.

### **Preventing and Managing Allergic Reactions**

Prior to administration of any dose of Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine, the healthcare provider should review the patient's prior immunization history for possible adverse events, to determine the existence of any contraindication to immunization with Influenza A (H1N1) 2009 Monovalent Vaccine and to allow an assessment of benefits and risks. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.



### **Limitations of Vaccine Effectiveness**

Vaccination with Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine may not protect all individuals.

### **ADVERSE REACTIONS**

The data in this section were obtained from clinical studies and postmarketing experience with FLUVIRIN. See product package insert for a complete list of adverse reactions.

### **Overall Adverse Reaction Profile**

Serious allergic reactions, including anaphylactic shock, have been observed in individuals receiving Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine during postmarketing surveillance.

### **Clinical Trial Experience**

Adverse event information from clinical trials provides a basis for identifying adverse events that appear to be related to vaccine use and for approximating the rates of these events. However, 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.

**Note: See manufacturer's information for more details regarding clinical trials.**

### **Postmarketing Experience**

The following additional adverse reactions have been reported during post-approval use of Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine. Because these reactions 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 vaccine exposure. Adverse events described here are included because: a) they represent reactions which are known to occur following immunizations generally or influenza immunizations specifically; b) they are potentially serious; or c) the frequency of reporting.

- *Body as a whole:* Local injection site reactions (including pain, pain limiting limb movement, redness, swelling, warmth, ecchymosis, induration), hot flashes/flushes; chills; fever; malaise; shivering; fatigue; asthenia; facial edema.
- *Immune system disorders:* Hypersensitivity reactions (including throat and/or mouth edema). In rare cases, hypersensitivity reactions have led to anaphylactic shock and death.
- *Cardiovascular disorders:* Vasculitis (in rare cases with transient renal involvement), syncope shortly after vaccination.
- *Digestive disorders:* Diarrhea; nausea; vomiting; abdominal pain.
- *Blood and lymphatic disorders:* Local lymphadenopathy; transient thrombocytopenia.
- *Metabolic and nutritional disorders:* Loss of appetite.
- *Musculoskeletal:* Arthralgia; myalgia; myasthenia.
- *Nervous system disorders:* Headache; dizziness; neuralgia; paraesthesia; confusion; febrile convulsions; Guillain-Barré Syndrome; myelitis (including

encephalomyelitis and transverse myelitis); neuropathy (including neuritis); paralysis (including Bell's Palsy).

- *Respiratory disorders:* Dyspnea; chest pain; cough; pharyngitis; rhinitis.
- *Skin and appendages:* Stevens-Johnson syndrome; sweating; pruritus; urticaria; rash (including non-specific, maculopapular, and vesiculobulbous).

## **OTHER ADVERSE REACTIONS ASSOCIATED WITH INFLUENZA VACCINATION**

Anaphylaxis has been reported after administration of FLUVIRIN. Although FLUVIRIN and Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine contain only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Allergic reactions include hives, angioedema, allergic asthma, and systemic anaphylaxis (see Contraindications).

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

## **DRUG INTERACTIONS**

### **Concomitant Administration with Other Vaccines**

There are no data to assess the concomitant administration of Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine with other vaccines. If Influenza A (H1N1) 2009 Monovalent Vaccine is to be given at the same time as another injectable vaccine(s), the vaccines should always be administered at different injection sites.

Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine should not be mixed with any other vaccine in the same syringe or vial.

### **Concurrent Use with Immunosuppressive Therapies**

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to Influenza A (H1N1) 2009 Monovalent Vaccine.

## **USE IN SPECIFIC POPULATIONS**

Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine and seasonal trivalent Influenza Virus Vaccine are manufactured by the same process.

### **Pregnancy**

Pregnancy Category C: Animal reproduction studies have not been conducted with Influenza A (H1N1) 2009 Monovalent Vaccine. It is also not known whether Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Influenza A (H1N1) 2009 Monovalent Vaccine should be given to a pregnant woman only if clearly needed.

### **Nursing Mothers**

It is not known whether Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Influenza A (H1N1) 2009 Monovalent Vaccine is administered to a nursing woman.

### **Pediatric Use**

Safety and effectiveness in pediatric subjects below the age of 4 years have not been established.

**Note: See manufacturer's information for details.**

### **Geriatric Use**

Since 1997, of the total number of geriatric subjects (n = 397) in clinical studies of Influenza A (H1N1) 2009 Monovalent Vaccine, 29% of adult subjects were 65 years and over, while 2.1% were 75 years and over.

Antibody responses were lower in the geriatric population than in younger subjects. Adverse events occurred less frequently in geriatric subjects ( $\geq 65$  years) than in younger adults. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

**Note: See manufacturer's information for details.**

## **DESCRIPTION**

Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine is a sub-unit (purified surface antigen) 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 neomycin and polymyxin. The influenza virus strain is harvested and clarified by centrifugation and filtration prior to inactivation with betapropiolactone. 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 nonylphenol ethoxylate, a process which removes most of the internal proteins. The nonylphenol ethoxylate is removed from the surface antigen preparation.

Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine is a homogenized, sterile, slightly opalescent suspension in a phosphate buffered saline. Influenza A (H1N1) 2009 Monovalent Vaccine is formulated to contain 15 mcg hemagglutinin (HA) per 0.5-mL dose of the following virus strain: A/California/7/2009 (H1N1)v-like virus.

The 0.5-mL prefilled syringe presentation is formulated without preservative. Thimerosal, a mercury derivative used during manufacturing, is removed by subsequent purification steps to a trace amount ( $\leq 1$  mcg mercury per 0.5-mL dose).

The 5-mL multidose vial formulation contains thimerosal, a mercury derivative, added as a preservative. Each 0.5-mL dose from the multidose vial contains 25 mcg mercury.

Each dose from the multidose vial or from the prefilled syringe may also contain residual amounts of egg proteins ( $\leq 1$  mcg ovalbumin), polymyxin ( $\leq 3.75$  mcg), neomycin ( $\leq 2.5$  mcg), betapropiolactone (not more than 0.5 mcg) and nonylphenol ethoxylate (not more than 0.015% w/v).

The multidose vial stopper and the syringe stopper/plunger do not contain latex.

## **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 post-vaccination with inactivated influenza virus vaccine have not been correlated with protection from influenza illness. In some human studies, antibody titer of  $\geq 1:40$  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.

## **NONCLINICAL TOXICOLOGY**

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

The Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

## **HOW SUPPLIED/STORAGE AND HANDLING**

### **How Supplied**

Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine is supplied as a 0.5-mL prefilled single dose syringe, package of 10 syringes per carton (NDC 66521-200-02).

Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine is supplied as a 5-mL multidose vial, individually packaged in a carton (NDC 66521-200-10).

### **Storage and Handling**

Store Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine refrigerated between 2° and 8°C (36° and 46°F).

- **Do not freeze.** Discard if the vaccine has been frozen.
- Store in the original package to protect from light.
- Do not use after the expiration date.
- Between uses, return the multidose vial to the recommended storage conditions.

## **PATIENT COUNSELING INFORMATION**

Vaccine recipients and guardians should be informed by their health care provider of the potential benefits and risks of immunization with Influenza A (H1N1) 2009 Monovalent Vaccine. When educating vaccine recipients and guardians regarding the potential side effects, clinicians should emphasize that Influenza A (H1N1) 2009 Monovalent Vaccine contains non-infectious particles and cannot cause influenza. The 2009 H1N1 Vaccine Information Statement (VIS) should be provided to the patient or parent/guardian.

Vaccine recipients and guardians should be instructed to report any severe or unusual adverse reactions to their healthcare provider.

Vaccine recipients should be advised that there are two influenza vaccine formulations for this influenza season, the monovalent pandemic (H1N1) 2009 influenza vaccine and seasonal trivalent influenza vaccine.

## **REFERENCES**

1. CDC, "Serum Cross-Reactive Antibody Response to a Novel Influenza A (H1N1) Virus After Vaccination with Seasonal Influenza Vaccine," *MMWR*, 2009; 58(19): 521-4.
2. Hannoun C, Megas F, Piercy J., *Immunogenicity and Protective Efficacy of Influenza Vaccination*, *Virus Res*, 2004; 103:133-138.
3. 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.
4. Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine Patient Package Insert.

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## **Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine, Injection**

Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine is an inactivated influenza virus vaccine indicated for active immunization of persons 6 months of age and older against influenza disease caused by pandemic (H1N1) 2009 virus. See Table 3 for dosage by age group.

<b>Table 3. Dosage by Age Group</b>	
<b>AGE GROUP</b>	<b>DOSAGE</b>
Children 6 through 35 months	Two 0.25 mL intramuscular doses approximately 1 month apart.
Children 36 months through 9 years	Two 0.5 mL intramuscular doses approximately 1 month apart
Children 10 years and older	One single 0.5 mL intramuscular dose.
Adults, 18 years and older	One single 0.5 mL intramuscular dose

### **ADMINISTRATION INSTRUCTIONS**

#### **Administration Instructions**

Inspect Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine syringes and vials visually for particulate matter and/or discoloration prior to administration. If either of these conditions exist, the vaccine should not be administered.

In children, the preferred sites for intramuscular injections are the anterolateral aspect of the thigh in infants or the deltoid muscle of the upper arm in toddlers and young children. The vaccine should not be injected into the gluteal region or into areas where there may be a major nerve trunk.

In adults, the preferred site for intramuscular injection is the deltoid muscle. The vaccine should not be injected into the gluteal region or into areas where there may be a major nerve trunk.

Shake the syringe and single-dose vials well before administering the vaccine and shake the multi-dose vial each time before withdrawing a dose of vaccine.

### **DOSAGE FORMS AND STRENGTHS**

Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine is a sterile suspension for intramuscular injection (see manufacturer's information on Description).

Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine is supplied in 4 presentations:

1. Prefilled syringe, 0.25 mL, no preservative, for 6 through 35 months of age; distinguished by a pink syringe plunger rod;
2. Prefilled syringe, 0.5 mL, no preservative, for 36 months of age and older;
3. Single-dose vial, 0.5 mL, no preservative, for 36 months of age and older;
4. Multi-dose vial, 5 mL, for 6 months of age and older, contains thimerosal, a mercury derivative, added as a preservative. Each 0.5 mL dose contains 25 micrograms (mcg) mercury.

## **CONTRAINDICATIONS**

### **Hypersensitivity**

Do not administer Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine to anyone with a known severe hypersensitivity to egg proteins, gelatin or any component of the vaccine or life-threatening reactions after previous administration of any influenza vaccine (see manufacturer's information on Warnings and Precautions, and Description).

## **WARNINGS AND PRECAUTIONS**

### **Guillain-Barré Syndrome**

Recurrence of Guillain-Barré syndrome (GBS) has been temporally associated with the administration of influenza vaccine. The decision to give Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine to individuals who have a prior history of Guillain-Barré syndrome should be based on careful consideration of the potential benefits and risks.

### **Altered Immunocompetence**

If Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished.

### **Preventing and Managing Allergic Reaction**

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

### **Limitations of Vaccine Effectiveness**

Vaccination with Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine may not protect all recipients.

## **ADVERSE REACTIONS**

Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine and seasonal trivalent Influenza Virus Vaccine (Fluzone®) are manufactured by the same process.

Adverse reaction information is based on studies conducted with seasonal trivalent Influenza Virus Vaccine.

Most common ( $\geq 10\%$ ) local reactions were soreness at injection site, tenderness, pain, and swelling.

Most common ( $\geq 10\%$ ) systemic events were malaise, headache, and myalgia.

For additional data, see Clinical Trial and Post-Marketing Experience below.

### **Clinical Trial Experience**

Adverse event information from clinical trials provides the basis for identifying adverse events that appear to be related to vaccine use and for approximating the rates of these events. However, because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trial of another vaccine, and may not reflect the rates observed in practice.

**Note: See manufacturer's information for more details regarding clinical trials.**

### **Post-Marketing Experience**

The following additional events have been reported during post-approval use of Fluzone vaccine. 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 vaccine exposure.

*Blood and Lymphatic System Disorders:* Thrombocytopenia, lymphadenopathy.

*Immune System Disorders:* Anaphylaxis, other allergic/hypersensitivity reactions (including urticaria, angioedema).

*Nervous System Disorders:* GBS, convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination), dizziness, paresthesia.

*Vascular Disorders:* Vasculitis, vasodilation/flushing

*Respiratory, Thoracic and Mediastinal Disorders:* Dyspnea, pharyngitis, rhinitis

*Skin and Subcutaneous Tissue Disorders:* Stevens-Johnson syndrome

*General Disorders and Administration Site Conditions:* Fever, pain, pruritis, asthenia/fatigue, pain in extremities, chest pain

## **OTHER ADVERSE EVENTS ASSOCIATED WITH INFLUENZA VACCINES**

Anaphylaxis has been reported after administration of influenza vaccines. Although Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine contains only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Allergic reactions include hives, angioedema, allergic asthma, and systemic anaphylaxis.

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.

## **DRUG INTERACTIONS**

### **Concomitant Administration with Other Vaccines**

There are no data on the concomitant administration of Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine with seasonal trivalent influenza vaccines.

Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine should not be mixed with any other vaccine in the same syringe or vial.

If Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine is to be given at the same time as another injectable vaccine(s), the vaccine(s) should always be administered at different injection sites.

### **Concurrent Immunosuppressive Therapies**

If Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine is administered to immunosuppressed persons or persons receiving immunosuppressive therapy, immunologic response may be diminished.

## **USE IN SPECIFIC POPULATIONS**

Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine and seasonal trivalent Influenza Virus Vaccine (Fluzone vaccine) are manufactured by the same process. Available information for Fluzone vaccine is provided in this section.

### **Pregnancy**

Pregnancy Category C: Animal reproduction studies have not been conducted with Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine or Fluzone vaccine. It is also not known whether these vaccines can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Influenza A (H1N1) 2009 Monovalent Vaccine should be given to a pregnant woman only if clearly needed.

### **Nursing Mothers**

It is not known whether Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine or Fluzone vaccine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when this vaccine is administered to a nursing woman.

### **Pediatric Use**

Safety and effectiveness in pediatric subjects below the age of 6 months have not been established. The immune response and safety of Fluzone vaccine was evaluated in 31 children between the ages of 6-26 months (see manufacturer's information on Adverse Reactions, and Clinical Studies).

### **Geriatric Use**

Immune response to Fluzone vaccine in subjects older than 61 years of age were lower when compared to immune responses in adults 19-59 years of age (see manufacturer's information on Clinical Studies).

### **DESCRIPTION**

Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine, an inactivated influenza virus vaccine, for intramuscular use, is prepared from influenza viruses propagated in embryonated chicken eggs. The virus-containing allantoic fluid is harvested and inactivated with formaldehyde. Influenza virus is concentrated and purified in a linear sucrose density gradient solution using a continuous flow centrifuge. The virus is then chemically disrupted using a non-ionic surfactant, polyethylene glycol p-isooctylphenyl ether (Triton® X-100), producing a "split virus". The split virus is further purified and then suspended in sodium phosphate-buffered isotonic sodium chloride solution.

Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine is formulated to contain 15 mcg hemagglutinin (HA) of influenza A/California/07/2009 (H1N1) v-like virus per 0.5 mL dose. Gelatin 0.05% is added as a stabilizer. Each 0.5 mL dose may contain residual amounts of formaldehyde (not more than 100 mcg), polyethylene glycol p-isooctylphenyl ether (not more than 0.02%), and sucrose (not more than 2.0%).

There is no thimerosal used in the manufacturing process of the single-dose presentations of Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine. The multi-dose presentation of Influenza A (H1N1) 2009 Monovalent Vaccine contains thimerosal, a mercury derivative, added as a preservative. Each 0.5 mL dose of the multidose presentation contains 25 mcg mercury.

Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine is a sterile clear to a slightly opalescent suspension.

Antibiotics are not used in the manufacture of Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine.

All presentations of Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine do not contain latex.

### **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 hemagglutinin inhibition (HI) antibody titer post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza virus infection. In some human studies, antibody titer of  $\geq 1:40$  have been associated with protection from influenza illness in up to 50% of subjects.

Antibodies against one influenza virus type or subtype confer limited or no protection against another. Furthermore, antibodies 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.

## **NON-CLINICAL TOXICOLOGY**

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Neither Fluzone vaccine nor Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine have been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

## **HOW SUPPLIED/STORAGE AND HANDLING**

### **How Supplied**

Single-dose prefilled syringe, without needle, 0.25 mL, package of 10 prefilled syringes per carton – Product No. NDC 49281-650-25.

Single-dose prefilled syringe, without needle, 0.25 mL, package of 25 prefilled syringes per carton – Product No. NDC 49281-650-70.

Single-dose prefilled syringe, without needle, 0.5 mL, package of 10 prefilled syringes per carton – Product No. NDC 49281-650-50.

Single-dose prefilled syringe, without needle, 0.5 mL, package of 25 prefilled syringes per carton – Product No. NDC 49281-650-90.

Single-dose vial, 0.5 mL, package of 10 vials per carton – Product No. NDC 49281-650-10.

Multi-dose vial, 5 mL, one vial per carton. The vial contains ten 0.5 mL doses – Product No. NDC 49281-640-15.

Vial stoppers and syringe plungers do not contain latex.

### **Storage and Handling**

Store all Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine presentations refrigerated at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Discard if vaccine has been frozen.

Between uses, return the multi-dose vial to the recommended storage conditions at 2° to 8°C (35° to 46°F).

Do not use after the expiration date shown on the label.

## **PATIENT COUNSELING INFORMATION**

- Inform vaccine recipients or guardians that Influenza A (H1N1) 2009 Monovalent Vaccine contains killed viruses and cannot cause influenza.
- Inform vaccine recipients or guardians that there are two influenza vaccine formulations for this influenza season, the monovalent vaccine against influenza

disease caused by pandemic (H1N1) 2009 virus and seasonal trivalent influenza vaccine.

- Instruct vaccine recipients or guardians to report any severe or unusual adverse reactions to their health care provider.
- The 2009 H1N1 Vaccine Statement should be provided to the patient or parent/guardian.

## REFERENCES

1. CDC, "Serum Cross-Reactive Antibody Response to a Novel Influenza A (H1N1) Virus After Vaccination with Seasonal Influenza Vaccine," *MMWR*, 2009, 58(19):521-524.
2. CDC, "Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP)," *MMWR*, 2009, 58(RR08):1-52.
3. Sanofi Pasteur Inc. Data on file, 071107.
4. Hannoun C., et al., "Immunogenicity and Protective Efficacy of Influenza Vaccination," *Virus Res*, 2004, 03:133-138.
5. Hobson D., et al., "The Role of Serum Hemagglutinin-Inhibiting Antibody in Protection Against Challenge Infection with Influenza A2 and B viruses," *J Hyg Camb*, 1972; 70:767-777.
6. Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine Injection Patient Package Insert.

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**CSL's Influenza A (H1N1) 2009 Monovalent Vaccine, Injection (revised 11-16-09)**

CSL's Influenza A (H1N1) 2009 Monovalent Vaccine is an inactivated influenza virus vaccine indicated for active immunization of persons age **6 months** and older against influenza disease caused by pandemic (H1N1) 2009 virus. See Table 4 for dosage schedule by age group.

<b>Table 4. Dosage by Age Group</b>	
<b>AGE GROUP</b>	<b>DOSAGE</b>
<b>Children , 6 months through 35 months of age</b>	<b>Two 0.25 mL intramuscular doses approximately 4 weeks apart</b>
<b>Children , 36 months through 9 years of age</b>	<b>Two 0.5 mL intramuscular doses approximately 4 weeks apart</b>
<b>Children, 10 years of age and older</b>	<b>A single 0.5 mL dose for intramuscular dose</b>
<b>Adults, 18 years and older</b>	<b>One single 0.5 mL intramuscular dose</b>

**ADMINISTRATION INSTRUCTIONS**

**Administration Instructions**

CSL's Influenza A (H1N1) 2009 Monovalent Vaccine syringes and vials should be inspected visually for particulate matter and discoloration prior to administration, whenever suspension and container permit. If either of these conditions exists, the vaccine should not be administered. Any vaccine that has been frozen or is suspected of being frozen must not be used.

When using the preservative-free, single-dose syringe, shake the syringe thoroughly and administer the dose immediately.

When using the multi-dose vial, shake the vial thoroughly before withdrawing each dose, and administer the dose immediately. Between uses, store the vial at 2–8°C (36–46°F)

Once the stopper has been pierced, the vial must be discarded within 28 days.

The preferred site for intramuscular injection is the deltoid muscle of the upper arm.

## DOSAGE FORMS AND STRENGTHS

CSL's Influenza A (H1N1) 2009 Monovalent Vaccine is a sterile suspension for intramuscular injection.

CSL's Influenza A (H1N1) 2009 Monovalent Vaccine is supplied in **three** presentations:

- **0.25 mL single-dose, pre-filled syringe, no preservative.**
- **0.5 mL single-dose, pre-filled syringe, no preservative.**
- **5 mL multi-dose vial containing ten doses. Thimerosal, a mercury derivative, is added as a preservative; each 0.5 mL dose contains 24.5 mcg of mercury.**

## CONTRAINDICATIONS

### Hypersensitivity

CSL's Influenza A (H1N1) 2009 Monovalent Vaccine is contraindicated in individuals with known hypersensitivity to eggs or chicken protein, neomycin, or polymyxin, or in anyone who has had a life-threatening reaction to previous influenza vaccination.

## WARNINGS AND PRECAUTIONS

### Guillain-Barré Syndrome (GBS)

If GBS has occurred within 6 weeks of previous influenza vaccination, the decision to give CSL's Influenza A (H1N1) 2009 Monovalent Vaccine should be based on careful consideration of the potential benefits and risks.

### Altered Immunocompetence

If CSL's Influenza A (H1N1) 2009 Monovalent Vaccine is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished.

### Preventing and Managing Allergic Reactions

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

### Limitations of Vaccine Effectiveness

Vaccination with CSL's Influenza A (H1N1) 2009 Monovalent Vaccine may not protect all individuals.

## ADVERSE REACTIONS

CSL's Influenza A (H1N1) 2009 Monovalent Vaccine and seasonal trivalent Influenza Virus Vaccine (AFLURIA) are manufactured by the same process.

Adverse reaction information is based on studies conducted with seasonal trivalent Influenza Virus Vaccine (AFLURIA). See manufacturer's information on Adverse Reactions.

## **Postmarketing Experience**

Because postmarketing reporting of adverse reactions 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 reactions described have been included in this section because they: 1) represent reactions that are known to occur following immunizations generally or influenza immunizations specifically; 2) are potentially serious; or 3) have been reported frequently. The following adverse reactions also include those identified during postapproval use of AFLURIA outside the US since 1985.

*Blood and lymphatic system disorders:* Transient thrombocytopenia

*Immune system disorders:* Allergic reactions including anaphylactic shock and serum sickness

*Nervous system disorders:* *Neuralgia*, paresthesia, and convulsions; encephalopathy, neuritis or neuropathy, transverse myelitis, and GBS

*Vascular disorders:* *Vasculitis* with transient renal involvement

*Skin and subcutaneous tissue disorders:* *Pruritis*, urticaria, and rash

*General disorders and administration site conditions:* Influenza-like illness (e.g., pyrexia, chills, headache, malaise, myalgia), injection-site inflammation (e.g., pain, erythema, swelling, warmth), and induration

## **OTHER ADVERSE EVENTS ASSOCIATED WITH INFLUENZA VACCINES**

Anaphylaxis has been reported after administration of AFLURIA. Although AFLURIA and CSL's Influenza A (H1N1) 2009 Monovalent Vaccine contain only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Allergic reactions include hives, angioedema, allergic asthma, and systemic anaphylaxis.

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 one additional case per 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 polyangiitis (vasculitis) has been reported temporally associated with influenza vaccination.

## **DRUG INTERACTIONS**

### **Concomitant Administration With Other Vaccines**

There are no data to assess the concomitant administration of CSL's Influenza A (H1N1) 2009 Monovalent Vaccine with other vaccines.

If CSL's Influenza A (H1N1) 2009 Monovalent Vaccine is to be given at the same time as another injectable vaccine(s), the vaccine(s) should be administered at different injection sites.

CSL's Influenza A (H1N1) 2009 Monovalent Vaccine should not be mixed with any other vaccine in the same syringe or vial.

### **Concurrent Immunosuppressive Therapies**

The immunological response to CSL's Influenza A (H1N1) 2009 Monovalent Vaccine may be diminished in individuals receiving corticosteroid or immunosuppressive therapies.

## **USE IN SPECIFIC POPULATIONS**

CSL's Influenza A (H1N1) 2009 Monovalent Vaccine and seasonal trivalent Influenza Virus Vaccine (AFLURIA) are manufactured by the same process. Available information for AFLURIA is provided in this section.

### **Pregnancy**

Pregnancy Category C: Animal reproduction studies have not been conducted with CSL's Influenza A (H1N1) 2009 Monovalent Vaccine or AFLURIA. It is also not known whether these vaccines can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. CSL's Influenza A (H1N1) 2009 Monovalent Vaccine should be given to a pregnant woman only if clearly needed.

### **Nursing Mothers**

Neither CSL's Influenza A (H1N1) 2009 Monovalent Vaccine nor AFLURIA has been evaluated in nursing mothers. It is not known whether Influenza A (H1N1) 2009 Monovalent Vaccine or AFLURIA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CSL's Influenza A (H1N1) 2009 Monovalent Vaccine is administered to a nursing woman.

### **Pediatric Use**

**Safety and effectiveness of CSL's Influenza A (H1N1) 2009 Monovalent Vaccine and AFLURIA in children below 6 months of age have not been established. The safety and immunogenicity of AFLURIA was evaluated in 298 children between the ages of 6 months and 9 years .**

### **Geriatric Use**

In four clinical studies, 343 subjects ages 65 years and older received AFLURIA. Hemagglutination-inhibiting (HI) antibody responses in geriatric subjects were lower after administration of AFLURIA in comparison to younger adult subjects (*see manufacturer's information on Clinical Studies*). Adverse event rates were generally similar in frequency to those reported in subjects ages 18 to less than 65 years, although some differences were observed.

## **DESCRIPTION**

CSL's Influenza A (H1N1) 2009 Monovalent Vaccine, for intramuscular injection, is a sterile, clear, colorless to slightly opalescent suspension with some sediment that resuspends upon

shaking to form a homogeneous suspension. CSL's Influenza A (H1N1) 2009 Monovalent Vaccine is prepared from influenza virus propagated in the allantoic fluid of embryonated chicken eggs. Following harvest, the virus is purified in a sucrose density gradient using a continuous flow zonal centrifuge. The purified virus is inactivated with beta-propiolactone, and the virus particles are disrupted using sodium taurodeoxycholate to produce a "split virion". The disrupted virus is further purified and suspended in a phosphate buffered isotonic solution.

CSL's Influenza A (H1N1) 2009 Monovalent Vaccine is formulated to contain 15 mcg HA per 0.5 mL dose of influenza A/California/7/2009 (H1N1)v-like virus.

**Thimerosal, a mercury derivative, is not used in the manufacturing process for the single dose presentations; therefore these products contain no preservative. The multi-dose presentation contains thimerosal, added as a preservative; each 0.5 mL dose contains 24.5 mcg of mercury.**

**A single 0.5 mL dose of CSL's Influenza A (H1N1) 2009 Monovalent Vaccine contains sodium chloride (4.1 mg), monobasic sodium phosphate (80 mcg), dibasic sodium phosphate (300 mcg), monobasic potassium phosphate (20 mcg), potassium chloride (20 mcg), and calcium chloride (1.5 mcg). A single 0.25 mL dose of CSL's Influenza A (H1N1) 2009 Monovalent Vaccine contains half of these quantities.** From the manufacturing process, each dose may also contain residual amounts of sodium taurodeoxycholate ( $\leq 10$  ppm), ovalbumin ( $\leq 1$  mcg), neomycin sulfate ( $\leq 0.2$  picograms [pg]), polymyxin B ( $\leq 0.03$  pg), and beta-propiolactone ( $< 25$  nanograms).

The rubber tip cap and plunger used for the preservative-free, single-dose syringes and the rubber stoppers used for the multi-dose vial contain no latex.

## **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) and influenza B viruses have been in global circulation. Specific levels of HI antibody titers post-vaccination with inactivated influenza virus vaccine have not been correlated with protection from influenza virus. In some human studies, 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 to one or more new strains in each year's influenza vaccine.

## **NONCLINICAL TOXICOLOGY**

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Neither CSL's Influenza A (H1N1) 2009 Monovalent Vaccine nor AFLURIA has been evaluated for carcinogenic or mutagenic potential or for impairment of fertility.

## HOW SUPPLIED/STORAGE AND HANDLING

Product Description	NDC Number
Package of ten 0.25 mL single-dose, prefilled syringes without needles	33332-519-25
Package of ten 0.5 mL single-dose, preservative-free, prefilled syringes <b>without needles</b>	33332-519-01
Package of one 5 mL multi-dose vial; the vial contains ten 0.5 mL doses	33332-629-10

Store refrigerated at 2–8°C (36–46°F). Do not freeze. Protect from light. Do not use CSL's Influenza A (H1N1) 2009 Monovalent Vaccine beyond the expiration date printed on the label.

## PATIENT COUNSELING INFORMATION

- Inform vaccine recipients that CSL's Influenza A (H1N1) 2009 Monovalent Vaccine is an inactivated vaccine that cannot cause influenza but rather stimulates the immune system to produce antibodies. **The full effect of the vaccine is generally achieved approximately 3 weeks after vaccination**
- Instruct vaccine recipients to report any severe or unusual adverse reactions to their healthcare provider.
- Inform vaccine recipients that there are two influenza vaccine formulations for this influenza season, the monovalent vaccine against influenza disease caused by pandemic (H1N1) 2009 influenza virus and seasonal trivalent influenza vaccine.
- The 2009 H1N1 Vaccine Statement should be provided to the patient or parent/guardian.

## REFERENCES

1. Hannoun C, Megas F, Piercy J, "Immunogenicity and Protective Efficacy of Influenza Vaccination," *Virus Res*, 2004;103:133-138.
2. Hobson D, Curry RL, Beare AS, et al., "The Role of Serum Hemagglutination-inhibiting Antibody in Protection Against Challenge Infection with Influenza A2 and B Viruses," *J Hyg Camb*, 1972; 70:767-777.
3. CSL's Influenza A (H1N1) 2009 Monovalent Vaccine Package Insert.

	AGE GROUP	DOSAGE	
<b><u>MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal</u></b>	Children 2 years through 9 years	2 doses (0.2 mL* each, approximately 1 month apart)	Live Vaccine
	Children, adolescents and adults age 10 through 49 years	1 dose (0.2 mL*)	
	*NOTE: Each 0.2 mL dose is administered as 0.1 mL per nostril.		
<b><u>Novartis' Influenza A (H1N1) 2009 Monovalent Vaccine, Injection</u></b>	Children 4 through 9 years of age	Two 0.5mL doses by intramuscular injection approximately 1 month apart	Inactivated Vaccine
	Children 10 through 17	A single 0.5mL dose by intramuscular injection.	
	18 years of age and older	A single 0.5mL dose by intramuscular injection, preferably in the region of the deltoid muscle of the upper arm	
<b><u>Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine, Injection</u></b>	Children 6 through 35 months	Two 0.25 mL intramuscular doses approximately 1 month apart.	Inactivated Vaccine
	Children 36 months through 9 years	Two 0.5 mL intramuscular doses approximately 1 month apart	
	Children 10 years and older	One single 0.5 mL intramuscular dose.	
	Adults, 18 years and older	One single 0.5 mL intramuscular dose	
<b><u>CSL's Influenza A (H1N1) 2009 Monovalent Vaccine, Injection</u></b>	Children , 6 months through 35 months of age	Two 0.25 mL intramuscular doses approximately 4 weeks apart	Inactivated Vaccine
	Children , 36 months through 9 years of age	Two 0.5 mL intramuscular doses approximately 4 weeks apart	
	Children, 10 years of age and older	A single 0.5 mL dose for intramuscular dose	
	Adults, 18 years and older	One single 0.5 mL intramuscular dose	