sanofi pasteur
Influenza Virus Vaccine, H5N1

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Influenza Virus Vaccine, H5N1, safely and effectively. See full prescribing information for Influenza Virus Vaccine, H5N1.

Influenza Virus Vaccine, H5N1
Suspension for Intramuscular Injection
Initial U.S. Approval: 2007

----------INDICATIONS AND USAGE----------

Influenza Virus Vaccine, H5N1, is an inactivated monovalent influenza virus vaccine, indicated for active immunization of persons 18 through 64 years of age at increased risk of exposure to the H5N1 influenza virus subtype contained in the vaccine (1, 2.2, 14).

----------DOSAGE AND ADMINISTRATION----------

- Immunization consists of two 1 mL (90 µg) intramuscular injections, a 1 mL dose given on day 1 followed by another 1 mL dose given approximately 28 days later (window 21 to 35 days) (2, 2.1, 2.2).

----------DOSAGE FORMS AND STRENGTHS----------

- Each 1 mL dose contains 90 micrograms (µg) of influenza virus hemagglutinin (HA) of strain A/Vietnam/1203/2004 (H5N1, clade 1) (2.2, 3, 11).
- Suspension in a 5 mL multi-dose vial, contains thimerosal, a mercury derivative (approximately 50 µg mercury/dose), added as a preservative (3, 11).

----------CONTRAINDICATIONS----------

- None (4)

----------WARNINGS AND PRECAUTIONS----------

- History of a hypersensitvity reaction to chicken or egg proteins or life-threatening reactions to previous influenza vaccinations (5.1).
- If Guillain-Barré syndrome (GBS) has occurred within six weeks of vaccination with influenza vaccine, the decision to give Influenza Virus Vaccine, H5N1, should be based on careful consideration of the benefits and risks (5.2).
- Immunocompromised persons may have a reduced immune response to Influenza Virus Vaccine, H5N1 (5.3).

----------ADVERSE REACTIONS----------

Most common (>10%) adverse reactions are pain at injection site, headache, malaise, and myalgia (6).

To report SUSPECTED ADVERSE REACTIONS, contact Sanofi Pasteur Inc., at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 and http://vaers.hhs.gov .

----------DRUG INTERACTIONS----------

- Do not mix with other vaccines in the same syringe or vial (7.1).
- Immunosuppressive therapies may reduce the immune response to Influenza Virus Vaccine, H5N1 (7.2).

----------USE IN SPECIFIC POPULATIONS-------

- Safety and effectiveness have not been established in pregnant or lactating women, and in pediatric and geriatric populations (8.1, 8.2, 8.3, 8.4).

See 17 for PATIENT_COUNSELING_INFORMATION

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION:

1. INDICATIONS AND USAGE

Influenza Virus Vaccine, H5N1, is an inactivated monovalent influenza virus vaccine, indicated for active immunization of persons 18 through 64 years of age at increased risk of exposure to the H5N1 influenza virus subtype contained in the vaccine. This indication is based on immune response and not on demonstration of decreased influenza disease after vaccination with Influenza Virus Vaccine, H5N1.

2. DOSAGE AND ADMINISTRATION

2.1. Preparation for Administration

Inspect Influenza Virus Vaccine, H5N1, vials visually for particulate matter and/or discoloration prior to administration. If either of those conditions exists, the vaccine should not be administered.

Shake the multi-dose vial vigorously each time before withdrawing a dose of vaccine. Between uses, return the multi-dose vial to the recommended storage conditions, at 2° to 8°C (35° to 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.

2.2. Recommended Dose and Schedule

Influenza Virus Vaccine, H5N1, should be administered as a 1 mL dose by intramuscular injection preferably in the lateral aspect of the deltoid muscle of the upper arm. The second 1 mL dose of vaccine should be administered approximately 28 days later (window 21 to 35 days). The vaccine should not be injected in the gluteal region or areas where there may be a major nerve trunk. A needle ≥1 inch is preferred because needles <1 inch might be of insufficient length to penetrate the muscle tissue in certain adults.

3. DOSAGE FORMS AND STRENGTHS

Influenza Virus Vaccine, H5N1, is available as a suspension in 5 mL multi-dose vials containing 5 doses. Each 1 mL dose is formulated to contain 90 micrograms (μg) hemagglutinin (HA) of the influenza virus strain A/Vietnam/1203/2004 (H5N1, clade 1) and not more than 98.2 μg of thimerosal (approximately 50 μg of mercury/dose). Thimerosal, a mercury derivative, is added as a preservative.

4. CONTRAINDICATIONS

None

5. WARNINGS AND PRECAUTIONS

5.1. Hypersensitivity

Influenza Virus Vaccine, H5N1, contains chicken and egg proteins. The decision to give Influenza Virus Vaccine, H5N1, to persons with known systemic hypersensitivity reactions to egg proteins or life-threatening reactions to previous influenza vaccinations should be based on careful considerations of risks and benefits.

5.2. Guillain-Barré Syndrome

If Guillan-Barré syndrome has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give Influenza Virus Vaccine, H5N1, should be based on careful consideration of the potential benefits and risks.

5.3. Altered Immunocompetence

If Influenza Virus Vaccine, H5N1, is administered to immunocompromised persons, including individuals receiving immunosuppressive therapy, the expected immune response may not be obtained.

5.4. Preventing and Managing Allergic Reactions

Prior to administration of Influenza Virus Vaccine, H5N1, the healthcare provider should review the patient's prior immunization history for possible adverse events, to allow an assessment of benefits and risks. Epinephrine injection (1:1,000) and other appropriate agents used for the

control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

6. ADVERSE REACTIONS

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 use.

6.1. Data from Clinical Studies

A randomized, placebo-controlled, double-blind, multicenter trial was conducted in the US. Healthy adults 18 through 64 years of age were carefully screened for the absence of chronic illnesses. A total number of 103 subjects (mean age: 39.4 years; age range 18 through 64 years; 53.4 % female, race: 81.6% White, 10.7% Black or African American, and 7.8% Asian) received an intramuscular injection of an investigational vaccine formulation of A/Vietnam/1203/2004 (H5N1, clade 1) containing 90 μg hemagglutinin and no preservative, followed by another injection of the same dose approximately 28 days later. Forty-eight (48) subjects received 0.5 mL intramuscular injection of saline placebo. All adverse events were collected following each of the 2 doses.

Four serious adverse events (SAEs), all considered unrelated to vaccine, occurred after vaccination including one death and three other SAEs (one each: menorrhagia, cerebrovascular event, and breast cancer).

The table below summarizes the frequencies of the solicited adverse reactions that were recorded following any vaccination.

Table 1: Frequencies of Solicited Reactions* within 7 Days After Any Vaccination

	Percent (%)				
	Placebo (N=48)	**7.5 µg (N=101)**	**15 µg (N=101)**	**45 µg (N=98)**	**90 µg (N=103)**
Local reactions					
Pain	18.8	27.7	44.6	61.2	73.8
Tenderness	27.1	30.7	43.6	57.1	69.9
Erythema/Redness	14.6	14.9	10.9	18.4	20.4
Induration/Swelling	8.3	7.9	7.9	10.2	14.6
Systemic reactions					
Headache	37.5	27.7	34.7	22.4	35.9
Malaise	29.2	23.8	25.7	13.3	22.3
Myalgia	29.2	12.9	19.8	15.3	15.5

	Percent (%)				
	Placebo (N=48)	**7.5 µg (N=101)**	**15 µg (N=101)**	**45 µg (N=98)**	**90 µg (N=103)**
Nausea	6.3	10.9	14.9	5.1	9.7
Fever	8.3	8.9	10.9	2.0	6.8

* All solicited events are considered to be reactions.

Note: Immediate reactions are included, except for immediate redness and swelling, as no severity grade was assigned

Most of the solicited injection site reactions were of mild to moderate severity and resolved within three days of vaccination. Most of the solicited systemic reactions were also of mild to moderate severity.

The table below summarizes the frequencies of the unsolicited adverse events that were recorded throughout the study.

Table 2: Unsolicited Adverse Events* ≥ 5% Reported after any Vaccination

	Percent (%)*				
	Placebo (N = 48	**7.5 µg (N = 101)**	**15 µg (N = 101)**	**45 µg (N = 98)**	**90 µg (N = 103)**
Gastrointestinal disorders					
Diarrhea	2.1	4.0	4.0	2.0	5.8

Infections and infestations					
Nasopharyngitis	8.3	4.0	4.0	1.0	1.9
Upper respiratory tract infection	4.2	5.0	2.0	2.0	1.9
Nervous system disorders					
Headache	2.1	1.0	5.0	3.1	2.9
Respiratory, thoracic and mediastinal disorders					
Nasal congestion	0	5.0	2.0	1.0	1.0
Pharyngolaryngeal pain	2.1	2.0	5.0	1.0	4.9
General disorders and administration site conditions					
Pyrexia	6.3	0	0	0	0

* For unsolicited events, the denominator for percentages is the number of vaccinated subjects for whom safety data are available (safety analysis set).

6.2. Adverse Events Associated with Influenza Vaccines

Anaphylaxis has been reported after administration of influenza vaccines. Although Influenza Virus Vaccine, H5N1, 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. [see WARNINGS AND PRECAUTIONS (5.1)]

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.

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 Administration with Other Vaccines

There are no data to assess the concomitant administration of Influenza Virus Vaccine, H5N1, with other vaccines. If Influenza Virus Vaccine, H5N1, is to be given at the same time as another injectable vaccine(s), the vaccines should always be administered at different injection sites. Influenza Virus Vaccine, H5N1, should not be mixed with any other vaccine in the same syringe or vial.

7.2. 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 Virus Vaccine, H5N1.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

PREGNANCY CATEGORY C

Animal reproductive studies have not been conducted with Influenza Virus Vaccine, H5N1. It is not known whether Influenza Virus Vaccine, H5N1, can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Influenza Virus Vaccine, H5N1, should be given to a pregnant woman only if clearly needed.

8.2. Nursing Mothers

It is not known whether Influenza Virus Vaccine, H5N1, is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Influenza Virus Vaccine, H5N1, is administered to a nursing mother.

8.3. Pediatric Use

No data are available for the pediatric population (ages less than 18 years). Safety and effectiveness of Influenza Virus Vaccine, H5N1, in pediatric populations have not been established.

8.4. Geriatric Use

Clinical studies of Influenza Virus Vaccine, H5N1, did not include subjects 65 years of age and older to determine whether they respond differently from younger subjects. Other reported clinical experience has identified differences in immune response between the elderly and younger patients to inactivated influenza vaccines.

11. DESCRIPTION

Influenza Virus Vaccine, H5N1, a monovalent type A inactivated vaccine for intramuscular use, is a sterile suspension prepared from influenza virus propagated in embryonated chicken eggs and is supplied in 5 mL multi-dose vials. The virus-containing fluids are harvested and inactivated with formaldehyde. The 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 nonionic surfactant, polyethylene glycol p-isooctylphenyl ether (Triton® X-100), producing a "split virus." The split virus is then further purified by chemical means and suspended in sodium phosphate-buffered isotonic sodium chloride solution.

Influenza Virus Vaccine, H5N1, is a clear and slightly opalescent suspension formulated to contain 90 µg hemagglutinin (HA) per 1.0 mL dose of the influenza virus strain A/Vietnam/1203/2004 (H5N1, clade 1). Porcine gelatin (500 µg/dose) is added as a stabilizer. Thimerosal, a mercury derivative, is added as a preservative. Each 1.0 mL dose is formulated to contain not more than 98.2 µg thimerosal (approximately 50 µg mercury/dose). Each dose may also contain residual amounts of formaldehyde (not more than 200 µg), Polyethylene Glycol p-Isooctylphenyl Ether (not more than 0.05%), and sucrose (not more than 2.0%).

No antibiotics are used in the manufacture of this vaccine. This presentation is latex-free.

Influenza Virus Vaccine, H5N1, is available as a suspension in 5 mL multi-dose vials containing 5 doses and should be administered as a 1 mL dose by intramuscular injection. [see DOSAGE AND ADMINISTRATION (2) and DOSAGE FORMS AND STRENGTHS (3)]

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

The mechanism of action of type A (H5N1) influenza virus vaccines is not well understood. Influenza vaccines induce antibodies against the viral hemagglutinin in the vaccine, thereby blocking viral attachment to human respiratory epithelial cells. Specific levels of hemagglutinin inhibition (HI) antibody titer post-vaccination with inactive influenza virus vaccines, including H5N1 influenza virus vaccines, have not been correlated with protection from influenza illness but the antibody titers have been used as a measure of vaccine activity. In some human challenge

studies of other influenza viruses, antibody titers of ≥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 little or no protection against viruses from other types or subtypes. 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 virological basis for seasonal epidemics and the reason for the usual change of one or more new strains in each year's influenza vaccine.

Global surveillance of influenza identifies yearly antigenic variants. An influenza pandemic occurs when humans have little or no immunity to an influenza virus strain and this virus strain is rapidly transmitted from human to human. Antigenic variants of H5N1 viruses have been in circulation in the avian species globally, with rare transmission to humans. However, these avian H5N1 viruses may acquire mutations that facilitate transmission among humans.

13. NON-CLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Influenza Virus Vaccine, H5N1, has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

14. CLINICAL STUDIES

A prospective, randomized, double-blinded, placebo-controlled, dose-ranging, Phase 1-2 study was conducted in 452 healthy subjects 18 through 64 years of age (mean age: 40.5 years; 46.5% female, race: 80.8% White, 8.4% Black or African American, and 11.5% Asian). Vaccine doses contained 7.5 µg, 15 µg, 45 µg, or 90 µg no preservative hemagglutinin of the strain A/Vietnam/1203/2004 (H5N1, clade 1). For the 90 µg dosage, a total of 103 subjects received a dose on day 1 given as a 1.0 mL intramuscular injection, followed by another injection of the 90 µg dosage approximately 28 days later. Forty-eight (48) subjects received 0.5 mL intramuscular injections of saline placebo on the same schedule.

The objectives of the study were to assess safety by collecting solicited and unsolicited adverse events, and to assess immunogenicity by measuring neutralizing and hemagglutination inhibition (HAI) antibody titers, and by determining the proportion achieving titer of $\geq$1:40 twenty-eight days after the second dose.

Safety results are summarized in Section 6.1.

Immunogenicity results were as follows:

Table 3: Immunogenicity 28 days After Vaccination 2

Dose group	Number tested	GMT (95% CI)	Percent Responding (95%CI)*	Percent achieving a titer of >1:40 (95% CI)
Placebo	48	5.5 (4.8, 6.2)	0 (0, 7)	2 (0, 11)
90 µg	99**	27.7 (20.3, 38.0)	43 (33, 54)	44 (34, 55)

* Response requires both a 4-fold or greater increase over baseline, and achievement of a 1:40 titer or greater by HAI

** Blood specimens were not obtained from 4 subjects.

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1. How Supplied

Influenza Virus Vaccine, H5N1, is supplied in a 5.0 mL multi-dose vial containing five 1.0 mL doses. (NDC 49281-600-01)

16.2. Storage Conditions and Shelf Life

Store in a refrigerator at 2° to 8° C (35° to 46 °F). **Do not freeze**.

Do not use vaccine after expiration date. Protect from light.

17. PATIENT COUNSELING INFORMATION

Patients, parents or guardians should be fully informed by their health care provider of the benefits and risks of immunization with Influenza Virus Vaccine, H5N1. When educating vaccine recipients and guardians regarding the potential side effects, clinicians should emphasize that Influenza Virus Vaccine, H5N1, contains non-infectious particles.

Patients, parents or guardians should be instructed to report any serious adverse reaction to their health care provider.

Product information

as of April 2007

Manufactured by:

Sanofi Pasteur Inc.

Swiftwater PA 18370 USA

Triton X-100 is a registered trademark of Union Carbide, Co.