

Influenza Virus Vaccine Fluvirin®

2008 - 2009 FORMULA

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**FLUVIRIN® (Influenza Virus Vaccine)
Suspension for Intramuscular Injection
2008-2009 Formula
Initial US Approval: 1988**

INDICATIONS AND USAGE

- FLUVIRIN® is an inactivated influenza virus vaccine indicated for active immunization of persons 4 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine (1).
- FLUVIRIN® is not indicated for children less than 4 years of age because there is evidence of diminished immune response in this age group (8.4).

DOSAGE AND ADMINISTRATION

- Children**
- 4 to 8 years of age:** 0.5-mL dose via intramuscular injection, one or two doses.
 - Previously unvaccinated children 4 to 8 years of age should receive two 0.5-mL doses, one on day 1 followed by another 0.5-mL injection at least 1 month later (2.2).
 - Children 4 to 8 years of age who have been previously vaccinated with one or two doses of any influenza virus vaccine should receive only one 0.5-mL dose (2.2).
 - 9 years and older:** A single 0.5-mL intramuscular injection (2.2).

Adults

- A single 0.5-mL intramuscular injection (2.2).

DOSAGE FORMS AND STRENGTHS

- FLUVIRIN®, a sterile suspension for intramuscular injection, is supplied in two presentations:
- Pre-filled syringe, 0.5-mL. Thimerosal, a mercury derivative used during manufacture, is removed by subsequent purification steps to a trace amount (≤ 1 mcg mercury per 0.5-mL dose). (3, 11)
 - Multidose vial, 5-mL. Contains thimerosal, a mercury derivative (25 mcg mercury per 0.5-mL dose). Thimerosal is added as a preservative. (3, 11)

Each 0.5-mL dose contains a total of 45 micrograms (mcg) of influenza virus hemagglutinin (HA) from each of the following 3 strains: A/Brisbane/59/2007(H1N1); A/Uruguay/716/2007 (H3N2), an A/Brisbane/10/2007-like strain; and B/Florida/4/2006. (3, 11)

CONTRAINDICATIONS

- History of systemic hypersensitivity reactions to egg proteins, or any other component of FLUVIRIN®, or life-threatening reactions to previous influenza vaccinations. (4.1, 11)

WARNINGS AND PRECAUTIONS

- If Guillain-Barré syndrome has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give FLUVIRIN® should be based on careful consideration of the potential benefits and risks. (5.1)
- Immunocompromised persons may have a reduced immune response to FLUVIRIN®. (5.2)

ADVERSE REACTIONS

The most frequently reported adverse reactions are mild hypersensitivity reactions (such as rash), local reactions at the injection site, and influenza-like symptoms. (6)

To report SUSPECTED ADVERSE REACTIONS contact Novartis Vaccines at 1-800-244-7668, or VAERS at 1-800-822-7967 and www.vaers.hhs.gov.

DRUG INTERACTIONS

- Do not mix with any other vaccine in the same syringe or vial. (7.1)
- Immunosuppressive therapies may reduce immune response to FLUVIRIN®. (7.2)

USE IN SPECIFIC POPULATIONS

- Safety and effectiveness of FLUVIRIN® have not been established in pregnant women, nursing mothers or children less than 4 years of age. (8.1, 8.3, 8.4)
- Antibody responses were lower in the geriatric population than in younger subjects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: July 2008

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FLUVIRIN® is an inactivated influenza virus vaccine indicated for immunization of persons 4 years of age and older against influenza virus disease caused by influenza virus subtypes A and type B contained in the vaccine. [see DOSAGE FORMS AND STRENGTHS (3)]
FLUVIRIN® is not indicated for children less than 4 years of age because there is evidence of diminished immune response in this age group.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration
Inspect FLUVIRIN® 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. Shake the syringe vigorously before administering the vaccine and shake the multi-dose 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.

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

2.2 Recommended Dose and Schedule

Children (4 to 17 years of age):
For children 4 to 8 years of age, who have not previously been vaccinated with an influenza vaccine, FLUVIRIN® should be given as a 0.5-mL intramuscular injection on day 1 followed by another 0.5-mL intramuscular injection at least 1 month later. If a child between the ages of 4 and 8 years does not receive a second dose of vaccine within the same

season, only one dose of vaccine should be administered the following season. (15.3)
Children, 4 to 8 years of age, who have been vaccinated in preceding year(s) with one or two doses of any influenza virus vaccine should receive only one dose. (15.3)
Children over the age of 9 should receive a single 0.5-mL intramuscular injection.

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.

Adults (18 years and older):

FLUVIRIN® 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. A needle of ≥ 1 inch is preferred because needles < 1 inch might be of insufficient length to penetrate muscle tissue in certain adults.

3 DOSAGE FORMS AND STRENGTHS

FLUVIRIN® is a sterile, suspension for intramuscular injection. Each 0.5-mL dose contains a total of 45 mcg hemagglutinin from the 3 influenza virus types in the vaccine. [see DESCRIPTION (1.1)]

FLUVIRIN® is available in two presentations:

- Pre-filled syringe, 0.5-mL. Thimerosal, a mercury derivative used during manufacture, is removed by subsequent purification steps to a trace amount (≤ 1 mcg mercury per 0.5-mL dose).
- 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.

4 CONTRAINDICATIONS

- Hypersensitivity**
FLUVIRIN® should not be administered to anyone with known systemic hypersensitivity reactions to egg proteins (eggs or egg products), or to

any component of FLUVIRIN®, or who has had a life-threatening reaction to previous influenza vaccinations.

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 FLUVIRIN® should be based on careful consideration of the potential benefits and risks.

5.2 Altered Immunocompetence

If FLUVIRIN® is administered to immunocompromised persons, including individuals receiving immunosuppressive therapy, the expected immune response may not be obtained.

5.3 Preventing and Managing Allergic Reactions

Prior to administration of any dose of FLUVIRIN®, 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 FLUVIRIN® 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.

5.4 Limitations of Vaccine Effectiveness

Vaccination with FLUVIRIN® may not protect all individuals.

6 ADVERSE REACTIONS

6.1 Overall Adverse Reaction Profile

Serious allergic reactions, including anaphylactic shock, have been observed in individuals receiving FLUVIRIN® during postmarketing surveillance.

6.2 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.

Adult and Geriatric Subjects

Safety data were collected in a total of 2768 adult and geriatric subjects (18 years of age and older) who have received FLUVIRIN® in 29 clinical studies since 1982.

In 9 clinical studies since 1997, among 1261 recipients of FLUVIRIN®, 745 (59%) were women; 1211 (96%) were White, 23 (2%) Asian, 15 (1%) Black and 12 (1%) other; 370 (29%) of subjects were elderly (≥ 65 years of age). All studies have been conducted in the UK, apart from a study run in the US in 2005-2006 where FLUVIRIN® was used as a comparator for an unlicensed vaccine.

After vaccination, the subjects were observed for 30 minutes for hypersensitivity or other immediate reactions. Subjects were instructed to complete a diary card for three days following immunization (i.e. Day 1 to 4) to collect local and systemic reactions (see Tables 1 and 2). All local and systemic adverse events were considered to be at least possibly related to the vaccine. Local and systemic reactions mostly began between day 1 and day 2. The overall adverse events reported in clinical trials since 1998 in at least 5% of the subjects are summarized in Table 3.

TABLE 1. Solicited Adverse Events in the First 72-96 Hours After Administration of FLUVIRIN® in Adult (18-64 years of age) and Geriatric (≥ 65 years of age) Subjects.

	1998-1999*§		1999-2000*§		2000-2001*§	
	18-64 yrs N = 66	≥ 65 yrs N = 44	18-64 yrs N = 76	≥ 65 yrs N = 34	18-64 yrs N = 75	≥ 65 yrs N = 35
Local Adverse Events						
Pain	16 (24%)	4 (9%)	16 (21%)	-	9 (12%)	-
Mass	7 (11%)	1 (2%)	4 (5%)	-	8 (11%)	1 (3%)
Inflammation	5 (8%)	2 (5%)	6 (8%)	-	7 (9%)	1 (3%)
Echymosis	4 (6%)	1 (2%)	3 (4%)	1 (3%)	4 (5%)	-
Edema	2 (3%)	1 (2%)	1 (1%)	2 (6%)	3 (4%)	1 (3%)
Reaction	2 (3%)	-	2 (3%)	-	4 (5%)	1 (3%)
Hemorrhage	-	-	1 (1%)	-	-	-
Systemic Adverse Events						
Headache	7 (11%)	1 (2%)	17 (22%)	3 (9%)	4 (5%)	-
Fatigue	3 (5%)	2 (5%)	4 (5%)	1 (3%)	3 (4%)	-
Malaise	2 (3%)	1 (2%)	2 (3%)	1 (3%)	1 (1%)	-
Myalgia	1 (2%)	-	2 (3%)	-	-	-
Fever	1 (2%)	-	1 (1%)	-	-	-
Arthralgia	-	1 (2%)	-	1 (3%)	-	-
Sweating	-	-	3 (4%)	-	1 (1%)	1 (3%)

	2001-2002*^		2002-2003*^		2004-2005*^	
	18-64 yrs N = 75	≥ 65 yrs N = 35	18-64 yrs N = 107	≥ 65 yrs N = 88	18-64 yrs N = 74	≥ 65 yrs N = 61
Local Adverse Events						
Pain	12 (16%)	1 (3%)	14 (13%)	7 (8%)	15 (20%)	9 (15%)
Mass	4 (5%)	1 (3%)	-	-	2 (3%)	1 (2%)
Echymosis	2 (3%)	-	3 (3%)	2 (2%)	-	-
Edema	2 (3%)	1 (3%)	6 (6%)	2 (2%)	-	-
Erythema	5 (7%)	-	11 (10%)	5 (6%)	16 (22%)	5 (8%)
Swelling	-	-	-	-	11 (15%)	4 (7%)
Reaction	-	-	2 (2%)	-	-	-
Induration	-	-	14 (13%)	3 (3%)	11 (15%)	1 (2%)
Pruritus	-	-	1 (1%)	-	-	-
Systemic Adverse Events						
Headache	8 (11%)	1 (3%)	12 (11%)	9 (10%)	14 (19%)	3 (5%)
Fatigue	1 (1%)	1 (3%)	-	-	5 (7%)	2 (3%)
Malaise	3 (4%)	-	3 (3%)	4 (5%)	1 (1%)	1 (2%)
Myalgia	3 (4%)	-	5 (5%)	3 (3%)	8 (11%)	1 (2%)
Fever	-	-	-	1 (1%)	-	-
Arthralgia	-	-	2 (2%)	-	1 (1%)	-
Sweating	3 (4%)	1 (3%)	-	2 (2%)	-	-
Shivering	-	-	-	1 (1%)	-	-

Results reported to the nearest whole percent; Fever defined as $> 38^\circ\text{C}$

- not reported

* Solicited adverse events in the first 72 hours after administration of FLUVIRIN®

§ Solicited adverse events reported by COSTART preferred term

^ Solicited adverse events reported by MEDDRA preferred term

TABLE 2. Solicited Adverse Events in the First 72 Hours After Administration of FLUVIRIN® in Adult Subjects (18-49 years of age).

	2005-2006 US Trial FLUVIRIN® N = 304
Local Adverse Events	
Pain	168 (55%)
Erythema	48 (16%)
Echymosis	22 (7%)
Induration	19 (6%)
Swelling	16 (5%)
Systemic Adverse Events	
Headache	91 (30%)
Myalgia	64 (21%)
Malaise	58 (19%)
Fatigue	56 (18%)
Sore throat	23 (8%)
Chills	22 (7%)
Nausea	21 (7%)
Arthralgia	20 (7%)
Sweating	17 (6%)
Cough	18 (6%)
Wheezing	4 (1%)
Chest tightness	4 (1%)
Other difficulties breathing	3 (1%)
Facial edema	-

Results reported to the nearest whole percent

- not reported

TABLE 3. Adverse Events Reported by at least 5% of Subjects in Clinical Trials since 1998

	1998-1999*§		1999-2000*§		2000-2001*§	
	18-64 yrs N = 66	≥ 65 yrs N = 44	18-64 yrs N = 76	≥ 65 yrs N = 34	18-64 yrs N = 75	≥ 65 yrs N = 35
Adverse Events						
Fatigue	8 (12%)	2 (5%)	8 (11%)	2 (6%)	5 (7%)	-
Back pain	4 (6%)	3 (7%)	-	-	-	-
Cough increased	2 (3%)	2 (5%)	-	-	-	-
Echymosis	4 (6%)	1 (2%)	4 (5%)	1 (3%)	5 (7%)	-
Fever	3 (5%)	-	-	-	-	-
Headache	12 (18%)	5 (11%)	22 (29%)	5 (15%)	14 (19%)	2 (6%)
Infection	3 (5%)	2 (5%)	-	-	-	-
Malaise	4 (6%)	4 (9%)	4 (5%)	1 (3%)	-	-
Migraine	4 (6%)	1 (2%)	-	-	-	-
Myalgia	4 (6%)	1 (2%)	-	-	-	-
Sweating	5 (8%)	1 (2%)	-	-	-	-
Rhinitis	3 (5%)	1 (2%)	-	-	5 (7%)	2 (6%)
Pharyngitis	6 (9%)	1 (2%)	10 (13%)	-	6 (8%)	-
Arthralgia	-	-	-	2 (6%)	-	-
Injection site pain	16 (24%)	4 (9%)	16 (21%)	-	9 (12%)	-
Injection site ecchymosis	4 (6%)	1 (2%)	-	-	4 (5%)	-
Injection site mass	7 (11%)	1 (2%)	4 (5%)	-	8 (11%)	1 (3%)
Injection site edema	-	-	1 (1%)	2 (6%)	-	-
Injection site inflammation	5 (8%)	2 (5%)	6 (8%)	-	7 (9%)	1 (3%)
Injection site reaction	-	-	-	-	4 (5%)	1 (3%)

	2001-2002*^		2002-2003*^		2004-2005*^	
	18-64 yrs N = 75	≥ 65 yrs N = 35	18-64 yrs N = 107	≥ 65 yrs N = 88	18-64 yrs N = 74	≥ 65 yrs N = 61
Adverse Events						
Fatigue	5 (7%)	4 (11%)	11 (10%)	8 (9%)	4 (5%)	2 (3%)
Hypertension	-	-	1 (1%)	4 (5%)	-	-
Rhinorrhea	-	-	2 (2%)	5 (6%)	-	-
Headache	20 (27%)	2 (6%)	35 (33%)	18 (20%)	12 (16%)	1 (2%)
Malaise	6 (8%)	1 (3%)	13 (12%)	8 (9%)	-	-
Myalgia	4 (5%)	1 (3%)	10 (9%)	4 (5%)	-	-
Sweating	3 (4%)</					

FLUVIRIN[®], participants recorded their symptoms on a diary card during the three days after vaccination and noted any further symptoms they thought were attributable to the vaccine. The only reactions recorded were tenderness at the site of vaccination in 21% of the participants on day 1, which was still present in 16% on day 2 and 5% on day 3. In one child, the tenderness was also accompanied by redness at the site of injection for two days. The reactions were not age-dependent and there was no bias towards the younger children.

Three clinical studies were carried out between 1995 and 2004 in a total of 520 pediatric subjects (age range 6-47 months). Of these, 285 healthy subjects plus 41 'at risk' subjects received FLUVIRIN[®]. No serious adverse events were reported.

FLUVIRIN[®] should only be used for the immunization of persons aged 4 years and over.

6.3 Postmarketing Experience

The following additional adverse reactions have been reported during post-approval use of FLUVIRIN[®]. 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).

6.4 Other Adverse Reactions Associated with Influenza Vaccination

Anaphylaxis has been reported after administration of FLUVIRIN[®]. Although FLUVIRIN[®] 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 CONTRAINDICATIONS (4)].

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.

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

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

FLUVIRIN[®] should not be mixed with any other vaccine in the same syringe or vial.

7.2 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 FLUVIRIN[®].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with FLUVIRIN[®]. It is also not known whether FLUVIRIN[®] can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. FLUVIRIN[®] should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether FLUVIRIN[®] is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FLUVIRIN[®] is administered to a nursing woman.

8.4 Pediatric Use

The safety and immunogenicity of FLUVIRIN[®] have not been established in children under 4 years of age.

The safety and immunogenicity of FLUVIRIN[®] have been established in the age group 4 years to 16 years. The use of FLUVIRIN[®] in these age groups is supported by evidence from adequate and well controlled studies of FLUVIRIN[®] in adults that demonstrate the immunogenicity of FLUVIRIN[®] [see ADVERSE REACTIONS (6) and CLINICAL STUDIES (14)].

8.5 Geriatric Use

Since 1997, of the total number of geriatric subjects (n = 397) in clinical studies of FLUVIRIN[®], 29% 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 (≥65 years) than in younger adults. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. [see ADVERSE REACTION (6) and CLINICAL STUDIES (14)].

11 DESCRIPTION

FLUVIRIN[®] is a trivalent, 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. Each of the influenza virus strains is harvested and clarified separately 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.

FLUVIRIN[®] is a homogenized, sterile, slightly opalescent suspension

in a phosphate buffered saline. FLUVIRIN[®] has been standardized according to USPHS requirements for the 2008-2009 influenza season and is formulated to contain 45 mcg hemagglutinin (HA) per 0.5-mL dose in the recommended ratio of 15 mcg HA of each of the following 3 strains: A/Brisbane/59/2007 (H1N1); A/Uruguay/716/2007 (H3N2), an A/Brisbane/10/2007-like strain; and B/Florida/4/2006.

The 0.5-mL prefilled syringe presentation is formulated without preservative. However, thimerosal, a mercury derivative used during manufacturing, is removed by subsequent purification steps to a trace amount (≤ 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 (≤ 1 mcg ovalbumin), polymyxin (≤ 3.75 mcg), neomycin (≤ 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.

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 post-vaccination with inactivated influenza virus vaccine have not been correlated with protection from influenza illness. In some human studies, antibody titer of ≥1:40 have been associated with protection from influenza illness in up to 50% of subjects [see REFERENCES (15.1, 15.2)].

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 strains (i.e., 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 year [see REFERENCES (15.3)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

FLUVIRIN[®] has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

14 CLINICAL STUDIES

Between 1982 and 1991, twelve clinical studies were conducted in healthy adult and geriatric subjects and one in children between 4 and 12 years of age who were considered to be 'at risk'. Since 1991 an annual clinical study has been conducted in the UK in healthy adults aged 18 years or older. FLUVIRIN[®] was also used as a control in a US clinical trial in adults (18-49 years of age). In all the trials, blood samples were taken prior to vaccination and approximately three weeks after vaccination to assess the immunogenic response to vaccination by measurement of anti-HA antibodies.

Three clinical studies were carried out between 1995 and 2004 in a total of 520 pediatric subjects (age range 6-48 months). Of these, 285 healthy subjects plus 41 'at risk' pediatric subjects, received FLUVIRIN[®]. FLUVIRIN[®] should only be used for the immunization of persons aged 4 years and over.

14.1 Immunogenicity in Adults (18 to 64 years of age)

Tables 4 and 5 show the immunogenicity data for the adult age group. The seven clinical studies presented enrolled a total of 774 adult subjects. In the adult group, for all antigens (A/H1N1, A/H3N2 and B) at least one of the following point estimate criteria was met: the proportion of subjects with seroconversion (post-vaccination titer ≥1:40 from a pre-vaccination titer <1:10) or significant increase (at least a four-fold increase from pre-vaccination titer ≥1:10) in antibody titer was greater than 40%; the geometric mean titer (GMT) increase was >2.5; the proportion of subjects with a post-vaccination hemagglutination inhibition (HI) antibody titer ≥1:40 was greater than 70%.

TABLE 4. Summary of the Seroconversion and Proportion of Subjects Achieving an HI titer ≥1:40 for Adult Subjects

Year/Strain	No. of subjects	Seroconversion ^{***}			HI titer ≥1:40 [†]		
		N	%	95% CI ^{††}	N	%	95% CI ^{††}
1998-1999 A/H1N1 A/H3N2 B	66	48	73	(62, 83)	50	76	(65, 86)
		43	65	(54, 77)	47	71	(60, 82)
		42	64	(52, 75)	62	94	(88, 100)
1999-2000 A/H1N1 A/H3N2 B	76	45	59	(48, 70)	50	66	(55, 76)
		51	67	(57, 78)	66	87	(79, 94)
		53	70	(59, 80)	75	99	(96, 100)
2000-2001 A/H1N1 A/H3N2 B	74	41	55	(44, 67)	41	55	(44, 67)
		45	61	(50, 72)	52	70	(59, 81)
		50	68	(57, 78)	73	99	(96, 100)
2001-2002 A/H1N1 A/H3N2 B	75	44	59	(48, 70)	48	64	(53, 75)
		46	61	(50, 72)	68	91	(84, 97)
		42	56	(45, 67)	66	88	(81, 95)
2002-2003 A/H1N1 A/H3N2 B	106	62	58	(49, 68)	73	69	(60, 78)
		72	68	(59, 77)	93	88	(81, 94)
		78	74	(65, 82)	101	95	(91, 99)
2004-2005 A/H1N1 A/H3N2 B	74	52	70	(59, 80)	66	89	(80, 95)
		60	81	(70, 89)	73	99	(93, 100)
		57	77	(66, 86)	69	93	(85, 98)
2005-2006 A/H1N1 A/H3N2 B	303	191	63	(57, 68)	296	98	(95, 99)
		273	90	(86, 93)	294	97	(94, 99)
		213	70	(65, 75)	263	87	(82, 90)

^{***} Seroconversion: proportion of subjects with either a post-vaccination HI titer ≥1:40 from a pre-vaccination titer <1:10 or at least a four-fold increase from pre-vaccination HI titer ≥1:10 in antibody titer.

[†] HI titer ≥1:40: proportion of subjects with a post-vaccination titer ≥ 1:40.

^{††} 95% CI: 95% confidence interval

TABLE 5. Summary of the Geometric Mean Hemagglutination Inhibition Antibody Titers, Pre- and Post-Immunization, for Adult Subjects

Year/Strain	No. of subjects	Geometric Mean Titer (GMT)			
		Pre-vaccination	Post-vaccination	Fold Increase	(95% CI) [*]
1998-1999 A/H1N1 A/H3N2 B	66	7.26	160.87	22.16	(14.25, 34.46)
		8.23	87.02	10.57	(6.91, 16.16)
		20.97	231.07	110.2	(6.90, 17.59)
1999-2000 A/H1N1 A/H3N2 B	76	7.43	58.95	7.93	(5.73, 10.97)
		15.29	122.83	8.03	(5.80, 11.13)
		25.70	254.76	9.91	(6.97, 14.10)
2000-2001 A/H1N1 A/H3N2 B	74	5.42	33.80	6.24	(4.49, 8.69)
		15.98	126.01	7.89	(5.61, 11.09)
		26.24	308.25	11.75	(7.73, 17.85)
2001-2002 A/H1N1 A/H3N2 B	75	7.76	54.78	7.06	(5.24, 9.52)
		23.67	153.81	6.50	(4.78, 8.84)
		19.91	107.53	5.40	(3.95, 7.38)
2002-2003 A/H1N1 A/H3N2 B	106	7.78	60.39	7.77	(5.81, 10.39)
		23.32	292.03	12.52	(8.77, 17.87)
		30.20	314.11	10.40	(7.54, 14.34)
2004-2005 A/H1N1 A/H3N2 B	74	13	159	12	(8.39, 17)
		37	658	18	(12, 26)
		15	156	11	(7.87, 14)
2005-2006 A/H1N1 A/H3N2 B	303	29	232	8	(6.68, 9.59)
		14	221	15	(14, 17)
		13	83	6.5	(5.73, 7.37)

^{*} 95% CI: 95% confidence interval

14.2 Immunogenicity in Geriatric Subjects (65 years and over)

Tables 6 and 7 show the immunogenicity of FLUVIRIN[®] in the geriatric age group. The six clinical studies presented enrolled a total of 296 geriatric subjects. For each of the influenza antigens, the percentage of subjects who achieved seroconversion and the percentage of subjects who achieved HI titers of ≥1:40 are shown, as well as the fold increase in GMT.

For all antigens (A/H1N1, A/H3N2 and B) at least one of the following point estimate criteria was met: the proportion of subjects with seroconversion (post-vaccination titer ≥1:40 from a pre-vaccination titer <1:10) or significant increase (at least a four-fold increase from pre-vaccination titer ≥1:10) in antibody titer was greater than 30%; the geometric mean titer (GMT) increase was >2.0; the proportion of subjects with a post-vaccination hemagglutination inhibition (HI) antibody titer ≥1:40 was greater than 60%. The pre-specified efficacy criteria were met in each study, although a relatively lower immunogenicity of A/H1N1 strain was seen in the last four studies (the same strain was in each of the formulations).

TABLE 6. Summary of the Seroconversion and Proportion of Subjects Achieving an HI titer ≥1:40 for Geriatric Subjects

Year/Strain	No. of subjects	Seroconversion ^{***}			HI titer ≥1:40 [†]		
		N	%	95% CI ^{††}	N	%	95% CI ^{††}
1998-1999 A/H1N1 A/H3N2 B	42	33	79	(66, 91)	38	90	(82, 99)
		33	79	(66, 91)	36	86	(75, 96)
		13	31	(17, 45)	42	100	(100, 100)
1999-2000 A/H1N1 A/H3N2 B	34	10	29	(14, 45)	23	68	(52, 83)
		18	53	(36, 70)	31	91	(82, 100)
		9	26	(12, 41)	32	94	(86, 100)
2000-2001 A/H1N1 A/H3N2 B	35	5	14	(3, 26)	10	29	(14, 44)
		22	63	(47, 79)	31	89	(78, 99)
		13	37	(21, 53)	33	94	(87, 100)
2001-2002 A/H1N1 A/H3N2 B	35	5	14	(3, 26)	14	40	(24, 56)
		15	43	(26, 59)	33	94	(87, 100)
		6	17	(5, 30)	32	91	(82, 100)
2002-2003 A/H1N1 A/H3N2 B	89	24	27	(18, 36)	52	58	(48, 69)
		42	47	(37, 58)	85	96	(91, 100)
		41	46	(36, 56)	86	97	(93, 100)
2004-2005 A/H1N1 A/H3N2 B	61	17	28	(17, 41)	46	75	(63, 86)
		29	48	(35, 61)	60	98	(91, 100)
		38	62	(49, 74)	51	84	(72, 92)

^{***} Seroconversion: proportion of subjects with either a post-vaccination HI titer ≥1:40 from a pre-vaccination titer <1:10 or at least a four-fold increase from pre-vaccination HI titer ≥1:10 in antibody titer.

[†] HI titer ≥1:40: proportion of subjects with a post-vaccination titer ≥ 1:40

^{††} 95% CI: 95% confidence interval





TABLE 7. Summary of the Geometric Mean Hemagglutination Inhibition Antibody Titers, Pre- and Post-Immunization, for Geriatric Subjects

Year/Strain	No. of subjects	Geometric Mean Titer (GMT)			
		Pre-vaccination	Post-vaccination	Fold Increase	(95% CI) [*]
1998-1999 A/H1N1 A/H3N2 B	42	13.92	176.65	12.69	(8.24, 19.56)
		10.69	124.92	11.69	(7.02, 19.46)
		114.1	273.56	2.40	(1.82, 3.17)
1999-2000 A/H1N1 A/H3N2 B	34	15.82	50.58	3.20	(2.13, 4.80)
		28.00	133.19	4.76	(2.92, 7.76)
		57.16	127.86	2.24	(1.56, 3.20)
2000-2001 A/H1N1 A/H3N2 B	35	6.66	18.85	2.83	(1.91, 4.18)
		25.87	140.68	5.44	(3.72, 7.96)
		61.24	191.23	3.12	(2.13, 4.59)
2001-2002 A/H1N1 A/H3N2 B	35	12.69	26.65	2.10	(1.55, 2.84)
		47.33	114.26	2.41	(1.73, 3.38)
		45.49	91.89	2.02	(1.47, 2.78)
2002-2003 A/H1N1 A/H3N2 B	89	13.29	31.92	2.40	(1.90, 3.03)
		65.86	272.79	4.14	(3.09, 5.55)
		74.87	288.57	3.85	(2.89, 5.13)
2004-2005 A/H1N1 A/H3N2 B	61	21	64	3.13	(2.33, 4.2)
		72	320	4.43	(3.13, 6.27)
		20	114	5.69	(4.39, 7.38)

^{*} 95% CI: 95% confidence interval

14.3 Immunogenicity in Pediatric Subjects

A small-scale study, was conducted in 1987 to evaluate safety and immunogenicity of FLUVIRIN[®] in 38 'at risk' children, with diabetes and/or asthma, or lymphoid leukemia. Thirty-eight participants aged between 4 and 12 years of age were assessed. Ten subjects had diabetes, 21 had asthma,

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