- *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 lead 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 199 of the total number of geriatric subjects (n = 397) in clinical studies of FLUVIRIN®, 29% were 65 years and over, while 2.1% were 5 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. The 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 leaves 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 2012-2013 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 viruses:

A/Christchurch/16, NIB-74 (H1N1) (an A/California/7/2009-like virus); A/Victoria/361/2011, IVR-165 (H3N2); and B/Hubei-Wujiagang/158/2009, NYMC BX-39 (a B/ Wisconsin/1/2010-like virus).

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 tip caps of the FLUVIRIN® prefilled syringes may contain natural rubber latex. 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 6-47 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 5 and 6 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 5**
**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 | 66 | 48 | 73 | (62, 83) | 50 | 76 | (65, 86) |
| A/H3N2 | | 43 | 65 | (54, 77) | 47 | 71 | (60, 82) |
| B | | 42 | 64 | (52, 75) | 62 | 94 | (88, 100) |
| **1999-2000** | | | | | | | |
| A/H1N1 | 76 | 45 | 59 | (48, 70) | 50 | 66 | (55, 76) |
| A/H3N2 | | 51 | 67 | (57, 78) | 66 | 87 | (79, 94) |
| B | | 53 | 70 | (59, 80) | 75 | 99 | (96, 100) |
| **2000-2001** | | | | | | | |
| A/H1N1 | 74 | 41 | 55 | (44, 67) | 41 | 55 | (44, 67) |
| A/H3N2 | | 45 | 61 | (50, 72) | 52 | 84 | (75, 92) |
| B | | 50 | 68 | (57, 78) | 73 | 99 | (96, 100) |
| **2001-2002** | | | | | | | |
| A/H1N1 | 75 | 44 | 59 | (48, 70) | 48 | 64 | (53, 75) |
| A/H3N2 | | 46 | 61 | (50, 72) | 68 | 91 | (84, 97) |
| B | | 42 | 56 | (45, 67) | 66 | 88 | (81, 95) |
| **2002-2003** | | | | | | | |
| A/H1N1 | 106 | 62 | 58 | (49, 68) | 73 | 69 | (60, 78) |
| A/H3N2 | | 72 | 68 | (59, 77) | 93 | 88 | (81, 94) |
| B | | 78 | 74 | (65, 82) | 101 | 95 | (91, 99) |
| **2004-2005** | | | | | | | |
| A/H1N1 | 74 | 52 | 70 | (59, 80) | 66 | 89 | (80, 95) |
| A/H3N2 | | 60 | 81 | (70, 89) | 73 | 99 | (93, 100) |
| B | | 57 | 77 | (66, 86) | 69 | 93 | (85, 98) |
| **2005-2006** | | | | | | | |
| A/H1N1 | 303 | 191 | 63 | (57, 68) | 296 | 98 | (95, 99) |
| A/H3N2 | | 273 | 90 | (86, 93) | 294 | 97 | (94, 99) |
| B | | 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