## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted**
**Emulsion for Intramuscular Injection**
**Initial U.S. Approval: xxxx**

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

- Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted is a vaccine indicated for active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine. Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted is approved for use in persons 18 years of age and older at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine. (1)

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

**For intramuscular injection only.**

- The vaccination series is 2 doses (0.5 mL each) administered 21 days apart. (2.1)
- Add one vial of AS03 adjuvant to one vial of H5N1 antigen to formulate the vaccine. (2.2)

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

- An emulsion for injection supplied as 2 separate vials: a vial of H5N1 antigen and a vial of AS03 adjuvant that must be combined prior to administration. (3)
- After mixing, the resulting emulsion contains ten 0.5 mL doses. (3)

### ----------CONTRAINDICATIONS----------

History of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or after a previous dose of an influenza vaccine. (4)

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

- Hypersensitivity reactions can occur. Appropriate medical treatment and supervision should be available to manage hypersensitivity reactions following vaccine administration. (5.1)
- If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted should be based on careful consideration of potential benefits and risks. (5.2)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.3)

### ---------- ADVERSE REACTIONS ----------

The most common (≥10%) solicited local and general reactions reported in clinical trials were injection site pain (83%), muscle aches (45%), headache (35%), fatigue (34%), joint pain (25%), shivering (17%), sweating (11%), and injection site swelling (10%). (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.**

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

Safety and effectiveness have not been established in pregnant women, nursing mothers, or children. (8.1, 8.3, 8.4)

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: xx/xxxx**

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## FULL PRESCRIBING INFORMATION: CONTENTS*



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

## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted is indicated for active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine. Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted is approved for use in persons 18 years of age and older at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine.

## 2 DOSAGE AND ADMINISTRATION

**For intramuscular injection only.**

### 2.1 Dose and Schedule

The Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted vaccination series is 2 doses (0.5 mL each), administered 21 days apart.

### 2.2 Preparation for Administration

Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted is supplied as 2 separate vials that must be combined prior to administration: a vial of H5N1 antigen and a vial of AS03 adjuvant.

1. Place one vial of H5N1 antigen and one vial of AS03 adjuvant at room temperature for a minimum of 15 minutes.
2. Mix each vial by inversion and inspect visually for particulate matter and discoloration. If either of these conditions exists, the vial(s) should not be used.
3. Cleanse both vial stoppers and withdraw the entire contents of the AS03 adjuvant vial using a sterile syringe with a 23-gauge sterile needle and add it to the H5N1 antigen vial to formulate the vaccine. (If a 23-gauge needle is not available, use a 22-gauge or 21-gauge needle.)
4. Mix the vaccine thoroughly by inversion. After mixing, label the H5N1 antigen vial (now containing the vaccine) with the date and time mixed in the designated area on the vial label.
5. The resulting volume provides 10 doses (0.5 mL each).
6. After mixing, the vaccine may be stored at room temperature up to 30°C (86°F) or refrigerated between 2° and 8°C (36° and 46°F) for up to 24 hours *[see How Supplied/Storage and Handling (16)]*.

### 2.3 Administration

Administer the vaccine within 24 hours after combining the H5N1 antigen and AS03 adjuvant.

If after mixing, the vaccine is stored refrigerated, place the vaccine at room temperature for a minimum of 15 minutes prior to administration.

Mix the vaccine thoroughly by inversion before each administration. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

Use a sterile needle (23-gauge is recommended) and sterile syringe for each dose withdrawal from the multi-dose vial and for vaccine administration.

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

Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted should not be mixed with any other vaccine in the same syringe or vial.

## 3 DOSAGE FORMS AND STRENGTHS

Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted is an emulsion for injection supplied as 2 separate vials, a vial of H5N1 antigen and a vial of AS03 adjuvant, that must be combined before use. Once combined, the resulting volume provides 10 doses (0.5 mL each) in a multi-dose vial.

## 4 CONTRAINDICATIONS

Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted is contraindicated in individuals with known severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or after a previous dose of an influenza vaccine *[see Description (11)]*.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity

Hypersensitivity reactions can occur with administration of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted. Appropriate medical treatment, including epinephrine, and supervision should be available to manage possible anaphylactic reactions following administration of the vaccine *[see Description (11)]*.

### 5.2 Guillain-Barré Syndrome

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

### 5.3 Syncope

Syncope (fainting) can occur with administration of injectable vaccines, including Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

### 5.4 Limitations of Vaccine Effectiveness

Vaccination with Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted may not protect all susceptible individuals.

Vaccination with Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted may not be as effective in preventing disease caused by influenza A (H5N1) virus in immunosuppressed persons, including individuals receiving immunosuppressive therapy, as in immunocompetent persons.

## 6 ADVERSE REACTIONS

In adults, the most common (≥10%) solicited local reactions were injection site pain (83%) and swelling (10%); the most common solicited general adverse reactions were muscle aches (45%), headache (35%), fatigue (34%), joint pain (25%), shivering (17%), and sweating (11%).

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine, and may not reflect the rates observed in practice. It is possible that broad use of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted could reveal adverse reactions not observed in clinical trials.

In a randomized, placebo-controlled, observer-blind, multicenter study, conducted in the United States and Canada, 4,561 subjects 18 years of age and older received Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted (N = 3,422) or saline placebo (N = 1,139) as a 2-dose vaccination series. Among adults 18 through 64 years of age, the mean age was 39 years (range 18 through 64 years) and included 57% female subjects and 86% white subjects. Among adults ≥65 years of age, the mean age was 72 years (range 65 through 91 years) and included 55% female subjects and 94% white subjects.

Solicited Adverse Reactions: Data on adverse events were collected using standardized forms for 7 days following receipt of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted or placebo (i.e., day of vaccination and the next 6 days). The reported frequencies of solicited local and general adverse reactions are presented in Table 1.

**Table 1. Percentage of Subjects With Solicited Local and General Adverse Reactions Within 7 Days of Any Vaccination[a]**

| | Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted (N = 3,375-3,376) % | | | Saline Placebo (N = 1,122-1,123) % | | |
|---|---|---|---|---|---|---|
| | Any[b] | Grade 2[c] or 3[d] | Grade 3[d] | Any[b] | Grade 2[c] or 3[d] | Grade 3[d] |
| **Local** | | | | | | |
| Injection site pain | 83 | 37 | 5 | 20 | 4 | 1 |
| Injection site swelling | 10 | 3 | 0.1 | 1 | 0.3 | 0 |
| Injection site erythema | 9 | 2 | 0.1 | 1 | 0.1 | 0 |
| **General** | | | | | | |
| Myalgia | 45 | 21 | 3 | 21 | 7 | 2 |
| Headache | 35 | 15 | 3 | 28 | 10 | 2 |
| Fatigue | 34 | 16 | 3 | 23 | 9 | 2 |
| Arthralgia | 25 | 11 | 2 | 12 | 4 | 1 |
| Shivering | 17 | 7 | 2 | 10 | 5 | 1 |
| Sweating | 11 | 4 | 1 | 7 | 3 | 1 |
| Fever | 5 | 2 | 1 | 3 | 1 | 1 |

N = number of subjects who received at least one dose and for whom safety data were available.

[a] Within 7 days defined as day of vaccination or placebo injection and the next 6 days.

[b] Any fever defined as ≥100.4ºF (38.0ºC).

[c] Grade 2: Pain defined as pain on moving the limb which interferes with normal activities or requires repeated use of pain relievers. Swelling and erythema defined as >50 mm. Fever defined as ≥101.3ºF (38.5ºC). For all other reactions, defined as some interference with normal everyday activities or requires repeated use of pain relievers (for headache, joint pain or muscle aches).

[d] Grade 3: Pain defined as significant pain at rest; prevents normal activities as assessed by inability to attend/do work or school. Swelling and erythema defined as >100 mm. Fever defined as ≥102.2ºF (39.0ºC). All other reactions were defined as those that prevented normal everyday activities, as assessed by inability to attend/do work or school, or those that required intervention of a physician/healthcare provider.

Unsolicited Adverse Events: The incidence of unsolicited adverse events reported during the 21-day post-vaccination periods for subjects who received Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted (N = 3,422) or placebo (N = 1,139) was 38.5% and 35.2%, respectively. Events reported in the Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted group at a rate of ≥0.5% of subjects, and at a rate at least twice that of the placebo group were

injection site pruritus (1.8% vs. 0.4%), dizziness (1.4% vs. 0.7%), injection site warmth (1.3% vs. 0.2%), injection site reaction (0.6% vs. 0.2%), and rash (0.6% vs. 0.3%).

Serious Adverse Events (SAEs): SAEs were reported for 0.5% of recipients of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted (N = 3,422) and for 0.3% of placebo recipients (N = 1,139) through day 42 (21 days following the second dose of vaccine or placebo). During the approximately one-year safety follow-up (day 364), SAEs were reported for 3.3% of recipients of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted and for 4.1% of placebo recipients.

The following SAEs reported through day 182 in subjects who received Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted are noted due to a temporal association with vaccination or because no alternative plausible causes for the event were identified: cerebral vascular accidents on day 1 and day 9 following the second vaccine dose (n = 1), pulmonary embolism (n = 1) on day 21 following the first vaccine dose, and corneal transplant rejection (n = 1) 18 years post transplant on day 103 following the second vaccine dose.

The following additional SAEs reported through day 364 are noted because they were reported exclusively in subjects who received Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted and because no alternative plausible causes were identified: convulsion (n = 3) on days 35, 252, and 346 and thyroid cancer (n = 3) on days 21, 29, and 223.

Potential Immune-Mediated Diseases: Based on a pre-specified list of events, 14 new onset potential immune-mediated diseases were reported through day 364, for 13 subjects (0.4%) who received Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted (N = 3,422). An additional event was reported for 1 subject (0.09%) who received saline placebo (N = 1,139). Events reported following Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted included polymyalgia rheumatica (n = 2), psoriasis (n = 2), and 1 of each of the following: autoimmune hepatitis, celiac disease, cranial nerve IV palsy, Crohn's disease, erythema nodosum, facial palsy, radiculitis, rheumatoid arthritis, rheumatoid lung, and temporal arteritis. An additional case of psoriasis was reported following placebo.

## 6.2 Postmarketing Experience

There is no postmarketing experience following administration of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted.

Other influenza vaccines containing AS03 adjuvant, Influenza vaccine (A/California/7/2009 H1N1), manufactured by GlaxoSmithKline in Quebec, Canada and Influenza vaccine (A/California/7/2009 H1N1), manufactured by GlaxoSmithKline in Dresden, Germany, were administered outside the United States during the Influenza A 2009 (H1N1) pandemic. The following adverse events were identified.

Spontaneously Reported Events: Because spontaneously reported events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their incidence or to establish a causal relationship to the vaccine. 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) of the frequency of reporting.

*Immune System Disorders:* Anaphylaxis, allergic reactions.

*Nervous System Disorders:* Febrile convulsions, Guillain-Barré syndrome, narcolepsy, somnolence.

*Skin and Subcutaneous Tissue Disorders:* Angioedema, generalized skin reactions, urticaria.

*General Disorders and Administration Site Conditions:* Injection site reactions (including inflammation, mass, necrosis, and ulcer).

Narcolepsy: Epidemiological studies[1-7] in several European countries evaluated a potential association between an influenza vaccine containing AS03 adjuvant (Influenza vaccine [A/California/7/2009 H1N1], manufactured by GlaxoSmithKline in Dresden, Germany) and narcolepsy. Some published studies reported a 2.9- to 14.2-fold increase in the risk of narcolepsy, with or without cataplexy, among vaccinated children and adolescents (younger than 20 years of age), and a 2.2- to 5.5-fold increase among vaccinated adults 20 years of age and older, compared to individuals of the same age group who did not receive this H1N1 vaccine.[1-7] Approximately 3 to 8 additional cases of narcolepsy per 100,000 vaccinated children/adolescents and approximately 1 additional case per 100,000 vaccinated adults were estimated to occur based on data from some of these studies.[2,3,6,7] No increase in the risk of narcolepsy was reported in some studies.[1] The relevance of these findings on narcolepsy to the United States population or to the Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted is unknown.

# 7 DRUG INTERACTIONS

## 7.1 Concomitant Vaccine Administration

No data are available to evaluate the concomitant administration of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted with other vaccines.

## 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 A (H5N1) Virus Monovalent Vaccine, Adjuvanted.

# 8 USE IN SPECIFIC POPULATIONS

## 8.1 Pregnancy

Pregnancy Category B

A reproductive and developmental toxicity study performed in female rats revealed no evidence of impaired female fertility or harm to the fetus due to Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted. In this study, the effect of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted on embryo-fetal and pre-weaning development was evaluated. Animals were administered Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted by intramuscular injection once prior to gestation, during the period of organogenesis (gestation days 7, 9, and 12), later in pregnancy (gestation day 16) and during lactation (day 7),

0.2 mL/dose/rat (approximately 80-fold excess relative to the projected human dose on a body weight basis). No adverse effects on mating, female fertility, pregnancy, parturition, lactation parameters, and embryo-fetal or pre-weaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis.

There are, however, no adequate and well-controlled studies of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted in pregnant women.

Because animal reproduction studies are not always predictive of human response, Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted should be used during pregnancy only if clearly needed.

### 8.3 Nursing Mothers

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

### 8.4 Pediatric Use

Safety and effectiveness of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted in the pediatric population have not been established.

### 8.5 Geriatric Use

A clinical study of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted included 1,489 subjects 65 years of age and older. Of the total number of subjects in the clinical study, 32.6% were 65 years of age and older, while 9.8% were 75 years of age and older.

Although subjects 65 years of age and older had a lower immune response to Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted than subjects 18 through 64 years of age, the pre-specified targets for the immunogenicity endpoints were met in the geriatric subjects. *[See Clinical Studies (14.1).]* No clinically relevant differences in safety between subjects 65 years of age and older and younger subjects were observed. *[See Adverse Reactions (6.1).]*

## 11 DESCRIPTION

Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted, for intramuscular injection, is a non-infectious, 2-component monovalent, AS03-adjuvanted vaccine. The vaccine is supplied as a vial of inactivated, split-virion, A/H5N1 influenza antigen suspension and a vial of AS03 adjuvant emulsion that must be combined prior to administration.

The A/H5N1 antigen suspension of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted is manufactured according to the same process as that used to produce the antigens contained in FLULAVAL® (Influenza Virus Vaccine) and FLULAVAL QUADRIVALENT® (Influenza Virus Vaccine), which are unadjuvanted seasonal Influenza Virus Vaccines licensed in the United States. The H5N1 antigen is a sterile, translucent to whitish opalescent suspension in a phosphate-buffered saline solution that may sediment slightly. The sediment resuspends upon mixing by inversion to form a homogeneous suspension. The H5N1 antigen is prepared from virus propagated in the allantoic cavity of embryonated hen’s eggs. The virus is inactivated

with ultraviolet light treatment followed by formaldehyde treatment, purified by centrifugation, and disrupted with sodium deoxycholate. The AS03 adjuvant is a homogenized, sterile, whitish emulsion composed of squalene, DL-α-tocopherol and polysorbate 80.

The vaccine is prepared by combining the H5N1 antigen suspension with the AS03 adjuvant emulsion. After combining, the vaccine is a whitish emulsion, formulated to contain 3.75 mcg hemagglutinin (HA) of the influenza virus strain A/Indonesia/05/2005 (H5N1) per 0.5-mL dose (10 doses per multi-dose vial). Each 0.5-mL dose contains 5 mcg thimerosal, a mercury derivative, as a preservative (<2.5 mcg mercury), 10.69 mg squalene, 11.86 mg DL-α-tocopherol, 4.86 mg polysorbate 80. Each 0.5-mL dose may also contain residual amounts of ovalbumin (≤0.083 mcg), formaldehyde (≤12.5 mcg), and sodium deoxycholate (≤3.75 mcg) from the manufacturing process.

The vial stoppers are not made with natural rubber latex.

# 12 CLINICAL PHARMACOLOGY

## 12.1 Mechanism of Action

A specific post-vaccination hemagglutination-inhibition (HI) antibody titer has not been correlated with protection from H5N1 influenza illness; however, HI titers have been used as a measure of influenza vaccine activity. In some human challenge studies with other influenza viruses, antibody titers of ≥1:40 have been associated with protection from influenza illness in up to 50% of subjects.[8,9]

# 13 NONCLINICAL TOXICOLOGY

## 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted has not been evaluated for its carcinogenic or mutagenic potential. Vaccination of female rats with Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted, at doses shown to be immunogenic in the rat, had no effect on fertility.

# 14 CLINICAL STUDIES

The A/H5N1 antigen suspension of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted is manufactured according to the same process as that used to produce the antigens contained in FLULAVAL and FLULAVAL QUADRIVALENT, unadjuvanted seasonal influenza virus vaccines licensed in the United States. Effectiveness of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted was demonstrated based on serum HI antibody responses to Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted, and effectiveness of FLULAVAL and FLULAVAL QUADRIVALENT, including a demonstration of efficacy of FLULAVAL QUADRIVALENT in the prevention of influenza disease.[10,11]

## 14.1 Immunological Evaluation

In a randomized, placebo-controlled, observer-blind, multicenter study, conducted in the United States and Canada, 4,561 adult subjects were randomized 3:1, stratified by age (18 through 49 years, 50 through 64 years and ≥65 years) to Influenza A (H5N1) Virus Monovalent

Vaccine, Adjuvanted (N = 3,422) or a saline placebo (N = 1,139). Each group received a 2-dose series administered approximately 21 days apart (range 19 to 25 days). In the overall population, 56% of subjects were female and 88% were white; analyses of age groups 18 through 64 years of age (mean 39 years of age) and ≥65 years of age (mean 72 years of age) were conducted. In a subset of subjects, hemagglutination-inhibition (HI) antibody titers to the A/Indonesia/05/2005 (H5N1) strain were evaluated in sera obtained 21 days after the second dose with Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted or placebo.

Analyses of the following co-primary endpoints were performed for the hemagglutinin (HA) antigen: endpoint 1) assessment of the rates of seroconversion (defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer ≥1:10, or an increase in titer from <1:10 to ≥1:40), and endpoint 2) assessment of the proportion of subjects with HI antibody titers of ≥1:40 after vaccination. The pre-specified targets for the endpoints varied by age of subjects enrolled. For the rates of seroconversion, the pre-specified target was a lower bound for the 2-sided 95% confidence interval ≥40% for the 18 through 64 years of age group and ≥30% for the ≥65 years of age group. For the proportion of subjects with HI antibody titers of ≥1:40 after vaccination, the pre-specified target was a lower bound for the 2-sided 95% confidence interval ≥70% for the 18 through 64 years of age group and ≥60% for the ≥65 years of age group.

In the subset of subjects evaluated, serum HI antibody responses to Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted met the pre-specified seroconversion criteria, and also the pre-specified criteria for the proportion of subjects with HI titers ≥1:40 (Table 2).

**Table 2. Seroconversion Rates and Percentage of Subjects With HI Titers ≥1:40 Following Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted or Placebo (21 Days After Dose 2) (ATP Cohort for Immunogenicity)**

| | Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted % (95% CI) | Placebo % (95% CI) |
|---|---|---|
| **Subjects 18 through 64 Years of Age** | **N = 1,571** | **N = 76** |
| Seroconversion[a] | 90.8[b] (89.3, 92.2) | 1.3 (0.0, 7.1) |
| % With HI titers ≥1:40 | 90.8[c] (89.3, 92.2) | 1.3 (0.0, 7.1) |
| **Subjects ≥65 Years of Age** | **N = 396** | **N = 40** |
| Seroconversion[a] | 74.0[b] (69.4, 78.2) | 2.5 (0.1, 13.2) |
| % With HI titers ≥1:40 | 74.5[c] (69.9, 78.7) | 2.5 (0.1, 13.2) |

HI = hemagglutination-inhibition; ATP = according-to-protocol; CI = Confidence Interval.
ATP cohort for immunogenicity included a subset of subjects who received 2 doses of vaccine and had serum collections according to the protocol.

[a] Seroconversion defined as at least a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer ≥1:10, or an increase in titer from <1:10 to ≥1:40.

[b] For the rates of seroconversion, the pre-specified target was met based on a lower bound for the 2-sided 95% confidence interval ≥40% for the 18 through 64 years of age group and ≥30% for the ≥65 years of age group.

[c] For the proportion of subjects with HI antibody titers of ≥1:40 after vaccination, the pre-specified target was met based on a lower bound for the 2-sided 95% confidence interval ≥70% for the 18 through 64 years of age group and ≥60% for the ≥65 years of age group.

## 15 REFERENCES


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11. FLULAVAL QUADRIVALENT [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2013.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted is supplied as 2 separate vials: a larger vial of H5N1 antigen and a smaller vial of AS03 adjuvant; one vial of AS03 adjuvant must be added to one vial of H5N1 antigen before use. Once combined, the resulting volume provides 10 doses (0.5-mL each) in a multi-dose vial.

Supplied as:

NDC 58160-808-15 (Package containing one carton of H5N1 antigen vials and 2 cartons of adjuvant vials)

NDC 58160-804-01 H5N1 antigen vial in carton of 50 (58160-804-15)
NDC 58160-802-02 AS03 adjuvant vial in carton of 25 (58160-802-16)

Storage Before Mixing: Both H5N1 antigen and AS03 adjuvant vials should be stored refrigerated between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the vials have been frozen. Protect from light.

Storage After Mixing: Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted should be administered within 24 hours of combining. Once combined, the vaccine may be stored refrigerated between 2° and 8°C (36° and 46°F) or at room temperature up to 30°C (86°F) for up to 24 hours. Do not freeze. Discard if the vaccine has been frozen. Protect from light.

## 17 PATIENT COUNSELING INFORMATION

Vaccine Information Statements are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization to the vaccine recipient, parent, or guardian. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

Inform vaccine recipients, parents or guardians that/to:

- Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted contains a non-infectious killed virus and cannot cause influenza.
- Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted is only intended to prevent illness due to the influenza virus contained in the vaccine.
- it is important to complete the immunization series.
- the potential for adverse reactions that have been temporally associated with administration of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted or other vaccines containing similar components exists.
- report any adverse events to their healthcare provider and/or VAERS.




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