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: 2013

----------RECENT MAJOR CHANGES----------

Indications and Usage (1) xx/xxxx
Dosage and Administration (2.1) xx/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 (6 months 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.

Age	Dose	Schedule
6 months through 17 years	Two doses 0.25-mL each	Administer 21 days apart
18 years and older	Two doses 0.5-mL each	Administer 21 days apart

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)
- The adult dose is 0.5 mL and the pediatric dose is 0.25 mL**.** (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 ----------

- In adults, the most common solicited local and general reactions reported in clinical trials were injection site pain (83%) and muscle aches (45%), respectively. (6.1)
- In infants and children, the most common solicited local reaction reported in clinical trials was injection site pain: 47% (6 through 35 months), 71% (3 through 8 years), and 82% (9 through 17 years). The most common solicited general reactions were irritability (51% in 6 through 35 months, and 30% in 3 through 5 years) and muscle aches (35% in 6 through 8 years, and 42% in 9 through 17 years). (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.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: XX/XXXX

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 6 months 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 dose and schedule are presented in Table 1.

Table 1. Dose and Schedule for Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted

Age	Dose	Schedule
6 months through 17 years	Two doses 0.25-mL each	Administer 21 days apart
18 years and older	Two doses 0.5-mL each	Administer 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. Withdraw 0.5 mL for an adult dose or 0.25 mL for a pediatric dose.

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 sites for injection are the anterolateral thigh for infants aged 6 months through 11 months and the deltoid muscle of the upper arm for persons aged 1 year and older.

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, which must be combined before use. The adult dose is 0.5 mL and the pediatric dose is 0.25 mL.

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.

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

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 adults, the most common solicited local and general reactions were injection site pain (83%) and muscle aches (45%), respectively.

In infants and children, the most common solicited local reaction was injection site pain: 47% (6 through 35 months), 71% (3 through 8 years), and 82% (9 through 17 years). The most common solicited general reactions were irritability (51% in 6 through 35 months, and 30% in 3 through 5 years) and muscle aches (35% in 6 through 8 years, and 42% in 9 through 17 years).

Adults

In a randomized, placebo-controlled, observer-blind, multicenter study, conducted in the United States and Canada, 4,561 subjects aged 18 years 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 aged 18 through 64 years, the mean age was 39 years (range:

18 through 64 years) and included 57% female subjects and 86% white subjects. Among adults aged 65 years and older, 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 2.

Table 2. Percentage of Subjects with Solicited Local and General Adverse Reactions within 7 Days[a] of Any Vaccination in Adults

	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						
Muscle aches	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 swelling/erythema defined as >20 mm. Any fever defined as ≥100.4ºF (38.0ºC).

[c] Grade 2: Pain defined as pain on moving the limb that 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 incidences 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) were 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 (1 subject), pulmonary embolism (1 subject) on Day 21 following the first vaccine dose, and corneal transplant rejection (1 subject) 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 (3 subjects) on Days 35, 252, and 346 and thyroid cancer (3 subjects) 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 (2 subjects), psoriasis (2 subjects), 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.

Pediatric Age Group 6 Months through 17 Years

In a randomized, placebo-controlled, observer-blind, multicenter trial, conducted in the United States, Canada, and Thailand, 838 subjects aged 6 months through 17 years received Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted (n = 607) or saline placebo (n = 231) as a 2-dose vaccination series. In the overall population, the mean age was 7 years (range: 6 months through 17 years); 52% were male; 45% were white, 15% black, 36% Asian, and 4% other racial groups; 11% were Hispanic or Latino. An uncontrolled crossover study was subsequently conducted in which 155 subjects who initially received placebo, then received Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted as a 2-dose series.

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 Tables 3 through 5.

Table 3. Percentage of Subjects with Solicited Local and General Adverse Reactions within 7 Days[a] of Any Vaccination in Persons Aged 6 through 35 Months

	Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted %			**Saline Placebo %**		
	Any[b]	**Grade 2[c] or 3[d] or >20 mm**	**Grade 3[d] or >50 mm**	**Any[b]**	**Grade 2[c] or 3[d] or >20 mm**	**Grade 3[d] or >50 mm**
Local	**n = 196**	**n = 196**	**n = 196**	**n = 73**	**n = 73**	**n = 73**
Injection site pain	47.4	15.3	2.6	30.1	4.1	2.7
Injection site erythema	33.7	4.1	0.5	26.0	0	0
Injection site swelling	28.6	3.1	0.5	15.1	0	0
General						
Irritability/fussiness	50.5	16.3	4.1	39.7	15.1	2.7
Drowsiness	37.8	14.8	4.1	30.1	11.0	2.7
Loss of appetite	29.1	10.2	3.1	32.9	15.1	5.5
Fever	22.4	10.7	4.6	16.4	12.3	5.5

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 swelling/erythema defined as >0 mm. Any fever defined as ≥100.4ºF (38.0ºC).

[c] Grade 2: Pain defined as cries/protests to touch. Fever defined as ≥101.3ºF (38.5ºC). For all other reactions, defined as some interference with normal everyday activities.

[d] Grade 3: Pain defined as cries when limb moved/spontaneously painful. Fever defined as ≥102.2ºF (39.0ºC). Loss of appetite defined as not eating at all. For all other reactions, defined as those that prevented normal everyday activities.

Table 4. Percentage of Subjects with Solicited Local and General Adverse Reactions within 7 Days[a] of Any Vaccination in Persons Aged 3 through 8 Years

	Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted %			Saline Placebo %		
	Any[b]	Grade 2[c] or 3[d] or >20 mm	Grade 3[d] or >50 mm	Any[b]	Grade 2[c] or 3[d] or >20 mm	Grade 3[d] or >50 mm
Local	**n = 197**	**n = 197**	**n = 197**	**n = 76**	**n = 76**	**n = 76**
Injection site pain	71.1	24.4	5.1	38.2	2.6	0
Injection site erythema	31.0	5.6	2.0	13.2	0	0
Injection site swelling	27.9	7.1	2.0	18.4	1.3	1.3
General						
3 Years through 5 Years	**n = 98**	**n = 98**	**n = 98**	**n = 49**	**n = 49**	**n = 49**
Irritability/fussiness	29.6	7.1	2.0	22.4	4.1	0
Drowsiness	27.6	4.1	1.0	14.3	2.0	0
Loss of appetite	22.4	5.1	2.0	10.2	4.1	0
Fever	15.3	9.2	5.1	18.4	8.2	2.0
6 Years through 8 Years	**n = 99**	**n = 99**	**n = 99**	**n = 27**	**n = 27**	**n = 27**
Muscle aches	35.4	8.1	3.0	18.5	0	0
Headache	29.3	10.1	2.0	7.4	0	0
Fatigue	22.2	10.1	0	3.7	0	0
Gastrointestinal[e]	17.2	5.1	1.0	22.2	3.7	0
Joint pain	14.1	4.0	1.0	7.4	0	0
Sweating	6.1	0	0	0	0	0
Shivering	4.0	1.0	1.0	0	0	0
Fever	13.1	6.1	4.0	0	0	0

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 swelling/erythema defined as >0 mm. Any fever defined as ≥100.4ºF (38.0ºC).

[c] Grade 2: Pain defined as cries/protests to touch (for those younger than 6 years) or pain on moving the limb that interferes with normal activities or requires repeated use of pain relievers. 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 cries when limb moved/spontaneously painful (for those younger than 6 years) or significant pain at rest; prevents normal activities as assessed by inability to attend/do work or school. Fever defined as ≥102.2ºF (39.0ºC). Loss of appetite defined as not eating at all. For all other reactions, defined as those that prevented normal everyday

activities, as assessed by inability to attend/do work or school for those 6 years and older, or those that required intervention of a healthcare provider.

[e] Nausea, vomiting, diarrhea, and/or abdominal pain.

Table 5. Percentage of Subjects with Solicited Local and General Adverse Reactions within 7 Days[a] of Any Vaccination in Persons Aged 9 through 17 Years

	Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted %			Saline Placebo %		
	Any[b]	Grade 2[c] or 3[d] or >20 mm	Grade 3[d] or >50 mm	Any[b]	Grade 2[c] or 3[d] or >20 mm	Grade 3[d] or >50 mm
Local	**n = 210**	**n = 210**	**n = 210**	**n = 80**	**n = 80**	**n = 80**
Injection site pain	81.9	24.8	4.8	22.5	5.0	2.5
Injection site erythema	25.7	3.3	0.5	12.5	0	0
Injection site swelling	28.6	8.6	1.9	8.8	0	0
General						
Muscle aches	41.9	14.3	1.9	15.0	3.8	1.3
Headache	33.8	10.5	2.9	20.0	6.3	3.8
Fatigue	31.9	10.0	1.9	22.5	5.0	2.5
Joint pain	17.1	5.7	0.5	8.8	1.3	0
Gastrointestinal[e]	12.4	6.2	1.4	15.0	3.8	2.5
Shivering	10.0	3.3	0.5	8.8	3.8	1.3
Sweating	9.0	3.3	1.0	5.0	1.3	0
Fever	2.9	0.5	0.5	3.8	1.3	1.3

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 swelling/erythema defined as >0 mm. Any fever defined as ≥100.4ºF (38.0ºC).

[c] Grade 2: Pain defined as pain on moving the limb that interferes with normal activities or requires repeated use of pain relievers. 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. Fever defined as ≥102.2ºF (39.0ºC). For all other reactions, 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 healthcare provider.

[e] Nausea, vomiting, diarrhea, and/or abdominal pain.

Unsolicited Adverse Events: The incidences of unsolicited adverse events reported during the 21-day post-vaccination periods for subjects who received Influenza A (H5N1) Virus

Monovalent Vaccine, Adjuvanted (n = 607) or placebo (n = 231) were 39.4% and 42.0%, 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 all injection site reactions combined (1.6% vs. 0.4%), gastroenteritis (1.2% vs. 0.4%), eye infections (1.0% vs. 0.4%), varicella (0.7% vs. 0%), and fatigue (0.5% vs. 0%).

Serious Adverse Events (SAEs): SAEs were reported for 2 (0.3%) recipients of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted (n = 607) and for 0 placebo recipients (n = 231) through Day 42 (21 days following the second dose of vaccine or placebo). During the approximately one-year safety follow-up (Day 385), SAEs were reported for 8 (1.3%) subjects who received Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted, and for 4 (1.7%) subjects who received placebo. One SAE of febrile convulsion was reported on Day 11 following the first vaccine dose in a 30-month-old subject who received Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted; although no fever occurred during the first 7 days post-vaccination, febrile convulsion is noted due to the temporal association with vaccination and because no alternative plausible cause for the event is identified.

Potential Immune-Mediated Diseases: Based on a pre-specified list of events, one potential immune-mediated disease (alopecia) was reported through Day 385 in a subject who received Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted (n = 607). One event (Type 1 diabetes) was reported for one subject who received placebo (n = 231).

Uncontrolled Crossover Study: One hundred fifty-five subjects who initially received placebo, received a 2-dose series of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted in the crossover study. Two (1.3%) subjects reported SAEs, which were not related to vaccination, through the one-year safety follow-up (Day 385). No potential immune-mediated diseases were reported.

Additional Safety Experience with AS03-Adjuvanted Influenza Vaccine (H1N1) in the Pediatric Age Group 6 Months through 9 Years

In a randomized, controlled, observer-blind, multicenter trial, conducted in 8 countries outside of the U.S., a total of 6,145 subjects aged 6 months through 9 years were randomized 1:1:1 to receive: one dose of a non-US licensed influenza A (H1N1) virus vaccine adjuvanted with AS03 (manufactured by GlaxoSmithKline), two doses of the same vaccine administered 21 days apart, or two doses of a non-US licensed, unadjuvanted influenza A (H1N1) virus vaccine (manufactured by GlaxoSmithKline) administered 21 days apart.

Serious Adverse Events (SAEs): SAE rates in subjects who received the adjuvanted vaccine (one or two doses) and the unadjuvanted vaccine were similar (0.4 % in these groups through Day 42, and 3.5% and 3.3% in these groups, respectively, through Day 385). The following SAEs reported through Day 385 in subjects who received the adjuvanted vaccine are noted because no alternative plausible causes for the event were identified or due to the temporal association with vaccination. One death was reported within 42 days of any vaccination: a 6-

month-old with a prior episode of pneumonia developed symptoms described as pneumonia and asthma exacerbation beginning on Day 7 following the first dose of the adjuvanted vaccine and died of sepsis on Day 19. The following non-fatal SAEs were reported through Day 385: hepatitis and nasopharyngitis on Day 5 following vaccination (1 subject), appendicitis on Days 8 or 9 following vaccination (3 subjects), and papillary thyroid cancer on Day 84 following vaccination (1 subject).

Potential Immune-Mediated Diseases: Based on a pre-specified list of events, 7 subjects (0.2%) in the adjuvanted arms (n = 4,096) reported new-onset potential immune-mediated diseases through Day 385; four subjects (0.2%) in the unadjuvanted arms (n = 2,049) reported such events. Events reported following administration of the adjuvanted vaccine were alopecia areata (2 subjects), glomerulonephritis (2 subjects), hypothyroidism (2 subjects), and idiopathic thrombocytopenic purpura (1 subject). Events reported following administration of the unadjuvanted vaccine were glomerulonephritis (2 subjects), Guillain-Barré syndrome (1 subject), and erythema multiforme (1 subject).

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, paresthesia.

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), and a 2.2- to 5.5-fold increase among vaccinated adults aged 20 years and older, compared with 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

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

There are no data on Influenza A (H5N1) Virus Monovalent, Adjuvanted in pregnant women to inform the vaccine-associated risks.

A developmental toxicity study was performed in female rats administered Influenza A (H5N1) Virus Monovalent, Adjuvanted prior to mating, during gestation, and during lactation. The dose was 0.2 mL at each occasion (a single adult human dose is 0.5 mL). This study revealed no evidence of harm to the fetus or offspring (until weaning) due to Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted *[see Data]*.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk: There is limited information on the risk of H5N1 infection in pregnant women. However, pregnant women infected with pandemic H1N1 or with seasonal influenza are at increased risk of severe illness associated with influenza infection compared to non-pregnant women. Pregnant women with influenza may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.

Data

Animal Data: A developmental toxicity study was performed in female rats. Animals were administered Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted by intramuscular injection once prior to gestation, and on gestation Days 7, 9, 12, and 16. Some rats were administered an additional dose on lactation Day 7. The dose was 0.2 mL at each occasion (a single adult human dose is 0.5 mL). No adverse effects on pre-weaning development up to post-natal Day 25 were observed. There were no fetal malformations or variations observed due to the vaccine.

8.2 Lactation

Risk Summary

It is not known whether Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted is excreted in human milk. Data are not available to assess the effects of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted and any potential adverse effects on the breastfed child from Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted in infants younger than 6 months have not been established.

8.5 Geriatric Use

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

Although subjects aged 65 years and older had a lower immune response to Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted than subjects aged 18 through 64 years, 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 aged 65 years 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 Vaccine) and FLULAVAL QUADRIVALENT® (Influenza Vaccine), which are unadjuvanted seasonal influenza 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 to yellowish milky 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 to yellowish homogenous milky emulsion.

Each 0.5-mL adult dose contains 3.75 mcg hemagglutinin (HA) of the influenza virus strain A/Indonesia/05/2005 (H5N1); 5 mcg thimerosal, a mercury derivative, as a preservative (<2.5 mcg mercury); and AS03 adjuvant (10.69 mg squalene, 11.86 mg DL-α-tocopherol, and 4.86 mg polysorbate 80). Each 0.5-mL adult 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.

Each 0.25-mL pediatric dose contains 1.9 mcg hemagglutinin (HA) of the influenza virus strain A/Indonesia/05/2005 (H5N1), and half of the amounts of the other components in the adult dose (listed above).

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 carcinogenic or mutagenic potential, or male infertility in animals. Vaccination of female rats with Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted had no effect on fertility *[see Pregnancy (8.1)]*.

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 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.

14.1 Immunological Evaluation

Adults

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 aged 65 years and older) 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 (mean: 39 years) and aged 65 years and older (mean: 72 years) were conducted. In a subset of subjects, 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 age group 18 through 64 years and ≥30% for the age group 65 years and older. 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 age group 18 through 64 years and ≥60% for the age group 65 years and older.

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 6).

Table 6. 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 Aged 18 through 64 Years	**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 Aged 65 Years and Older	**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 age group 18 through 64 years and ≥30% for the age group 65 years and older.

[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 age group 18 through 64 years and ≥60% for the age group 65 years and older.

Pediatric Age Group 6 Months to 17 Years

In a randomized, placebo-controlled, observer-blind, multicenter trial conducted in the United States, Canada, and Thailand, 838 subjects were randomized in an 8:3 ratio, stratified by age (6 through 35 months, 3 through 8 years, and 9 through 17 years) to receive either Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted (n = 607) or a saline placebo (n = 231). Each group received a 2-dose series administered 21 days apart. Analyses of age groups 6 through 35 months (mean: 22 months), 3 through 8 years (mean: 6 years), and 9 through 17 years (mean: 13 years) were conducted. 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.

The primary endpoint was the proportion of subjects with HI antibody titers of ≥1:40 after vaccination for the hemagglutinin (HA) antigen. The pre-specified criterion for success was a lower bound for the 98.3% confidence interval ≥70% for any age stratum. Each age stratum was evaluated independently. Serum HI antibody responses to Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted met the pre-specified criteria for all age strata (Table 7).

Table 7. 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 at Day 42)

	Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted		**Placebo**	
Age Group	**n**	**% (98.3% CI)**	**n**	**% (98.3% CI)**
Subjects aged 6 through 35 months	175	100.0[a] (97.3, 100.0)	64	0 (0, 7.2)
Subjects aged 3 through 8 years	184	99.5[a] (96.3, 100)	71	0 (0, 6.5)
Subjects aged 9 through 17 years	203	99.0[a] (95.8, 99.9)	76	1.3 (0, 8.6)

HI = Hemagglutination-inhibition; ATP = According-to-protocol; CI = Confidence Interval.

n = Number of subjects with available results.

ATP cohort for immunogenicity included a subset of subjects who received 2 doses of vaccine and had serum collections according to the protocol.

[a] 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 98.3% confidence interval ≥70% for all 3 age strata.

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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 is 5 mL 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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