

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

AUDENZ (Influenza A (H5N1) Monovalent Vaccine, Adjuvanted) injectable emulsion for intramuscular use

Initial U.S. Approval: 2020

INDICATIONS AND USAGE

AUDENZ is an inactivated vaccine indicated for active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine. AUDENZ is approved for use in persons 6 months 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

Administer two doses (0.5 mL each) 21 days apart. (2)

DOSAGE FORMS AND STRENGTHS

Injectable emulsion is supplied in two presentations:

- 0.5 mL single-dose pre-filled syringe. (3, 11)
- 5 mL multi-dose vial containing 10 doses (each dose is 0.5 mL). (3, 11)

CONTRAINDICATIONS

History of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine, or after a previous dose of an influenza vaccine. (4, 11)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions can occur. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine. (5.1)
- If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give AUDENZ should be based on careful consideration of potential benefits and risks. (5.2)

ADVERSE REACTIONS

- In adults 18 through 64 years of age, the most common ($\geq 10\%$) solicited local and systemic reactions reported in clinical trials were injection site pain (64%), fatigue (25%), headache (25%), malaise (22%), myalgia (14%), arthralgia (10%), and nausea (10%). (6.1)
- In adults 65 years of age and older, the most common ($\geq 10\%$) solicited local and systemic reactions reported in clinical trials were injection site pain (36%), fatigue (20%), malaise (16%), headache (16%), and arthralgia (10%). (6.1)
- In infants and children, 6 months through 5 years of age, the most common ($\geq 10\%$) solicited local and systemic reactions reported in clinical trials were tenderness (56%), irritability (30%), sleepiness (25%), change in eating habits (18%), and fever (16%). (6.1)
- In children 6 through 17 years of age, the most common ($\geq 10\%$) solicited local and systemic reactions reported in clinical trials were injection site pain (68%), myalgia (30%), fatigue (27%), malaise (25%), headache (22%), loss of appetite (14%), nausea (13%), and arthralgia (13%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Seqirus at 1-855-358-8966 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: [11]/ [2021]

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AUDENZ™ is an inactivated vaccine indicated for active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine. AUDENZ is approved for use in persons 6 months of age and older at increased risk of exposure to the influenza A H5N1 virus subtype contained in the vaccine.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only

2.1 Dose and Schedule

Administer two doses of AUDENZ (0.5 mL each), 21 days apart.

2.2 Administration

Shake the syringe gently before use and shake the multi-dose vial gently each time before withdrawing a dose of vaccine. Between multi-dose vial uses, return to the recommended storage conditions of 2° to 8°C (36° to 46°F). AUDENZ has a milky-white appearance. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit [*see Description (11)*]. If either condition exists, AUDENZ should not be administered.

The vaccine should be administered by intramuscular injection. Do not inject the vaccine in the gluteal region or areas where there may be a major nerve trunk. For those over 12 months of age, the preferred injection site is the region of the deltoid muscle of the upper arm; for those 6 months through 11 months of age, the preferred injection site is the anterolateral thigh.

3 DOSAGE FORMS AND STRENGTHS

AUDENZ is an injectable emulsion for intramuscular use supplied in two presentations:

- 0.5 mL single-dose pre-filled syringe
- 5 mL multi-dose vial containing 10 doses (each dose is 0.5 mL).

4 CONTRAINDICATIONS

Do not administer AUDENZ to anyone with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine [*see Description (11)*] or after a previous dose of an influenza vaccine.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Appropriate medical treatment and supervision must be available to manage possible severe allergic reactions (e.g., anaphylaxis) following administration of the vaccine.

5.2 Guillain-Barré Syndrome

If Guillain-Barré syndrome (GBS) has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give AUDENZ should be based on careful consideration of the potential benefits and risks. The 1976 swine influenza vaccine was associated with an elevated risk of GBS. Evidence for a causal relationship of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than 1 additional case per 1 million persons vaccinated.¹

5.3 Limitations of Vaccine Effectiveness

Vaccination with AUDENZ may not protect all recipients.

Immunocompromised persons, including those receiving immunosuppressive therapy, may have a diminished immune response to AUDENZ.

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 AUDENZ could reveal adverse reactions not observed in clinical trials.

In adults 18 through 64 years of age, the most common ($\geq 10\%$) solicited local and systemic reactions reported in clinical trials were injection site pain (64%), fatigue (25%), headache (25%), malaise (22%), myalgia (14%), arthralgia (10%) and nausea (10%).

In adults 65 years of age and older, the most common ($\geq 10\%$) solicited local and systemic reactions reported in clinical trials were injection site pain (36%), fatigue (20%), malaise (16%), headache (16%), and arthralgia (10%).

In infants and children, 6 months through 5 years of age, the most common ($\geq 10\%$) solicited local and systemic reactions reported in clinical trials were tenderness (56%), irritability (30%), sleepiness (25%), change in eating habits (18%), and fever (16%).

In children 6 years through 17 years of age, the most common ($\geq 10\%$) solicited local and systemic reactions reported in clinical trials were injection site pain (68%), myalgia (30%), fatigue (27%), malaise (25%), headache (22%), loss of appetite (14%), nausea (13%), and arthralgia (13%).

Adults 18 years of age and older:

Clinical safety data for AUDENZ in adults (18 years of age and older) have been collected from three studies: Study 1 in adults 18 through 64 years of age (NCT01776541); Study 2 in adults 65 years of age and older (NCT01766921), and Study 3, a placebo-controlled trial in adults 18 years of age and older (NCT02839330). Subjects in all studies received 2 doses of AUDENZ, administered intramuscularly 21 days apart. In all three studies, solicited local and systemic adverse reactions were collected for 7 days and unsolicited adverse events were collected for 21 days following each vaccination. Serious adverse events (SAEs), adverse events of special interest (AESIs) (prospectively defined events representing potential immune-mediated conditions), new onset of chronic diseases (NOCDs) (adverse events leading to a new diagnosis of a chronic medical condition), and medically-attended adverse events (MAAEs) (leading to an unscheduled healthcare visit) were collected for one year following the final vaccination in each subject. The safety population includes 3,579 subjects who received at least one dose of AUDENZ. Of these, 1,683 were adults 18 through 64 years of age and 1,896 were adults 65 years of age and older.

Study 3 was a randomized, observer-blind, multicenter, controlled study conducted in the US, in adults 18 years of age and older. Subjects were randomized in a 3:1 ratio to receive two doses of either AUDENZ or saline placebo, 21 days apart. In total, 3,191 subjects (18 through 64 years: N=1,596; 65 years and older: N=1,595) in the safety population received at least one dose of AUDENZ (N=2,395) or placebo (N=796). The mean age of the subjects ≥ 18 years was 58 years, and included 45% male, 84% white, 13% black or African American, 1% Asian, fewer than 1% reported as other racial groups, and 92% non-Hispanic/non-Latinos.

Solicited Reactions:

In Study 3, the most commonly reported ($\geq 10\%$) solicited local and systemic reactions in adults 18 through 64 years within 7 days following administration of AUDENZ were injection site pain (64%), fatigue (25%), headache (25%), malaise (22%), myalgia (14%), arthralgia (10%), and nausea (10%). In adults 65 years of age and older, the most common ($\geq 10\%$) solicited local and systemic reactions reported within 7 days following administration of AUDENZ were injection site pain (36%), fatigue (20%), malaise (16%), headache (16%), and arthralgia (10%).

Tables 1 and 2 present the reported frequencies of pre-specified solicited local and systemic adverse reactions in Study 3, actively collected on standardized diary cards during the seven days following any vaccination (i.e., on the day of vaccination and for six days thereafter). Adults 65 years and older generally reported fewer solicited local and systemic reactions as compared to younger persons. The majority of solicited local and systemic adverse reactions were mild or moderate in intensity. Severe reactions in subjects receiving AUDENZ were reported in 1% or fewer subjects for each reaction. Other than injection site pain which occurred more frequently in AUDENZ recipients as compared to placebo, rates and severity were similar between treatment groups. Frequencies of adverse reactions were higher after the first dose than after the second dose. Most local and systemic reactions occurred within two or three days of vaccination and were less than three days in duration.

Table 1: Percentages of Subjects 18 through 64 Years of Age and 65 Years of Age and Older Reporting Solicited Local Adverse Reactions within 7 Days after Any Vaccination with AUDENZ or Saline Placebo (Study 3^a).

Solicited Local Adverse Reactions ^b (%)	Adults 18 through 64 years of age	Adults 18 through 64 years of age	Adults 65 years of age and older	Adults 65 years of age and older
	AUDENZ (N=1163) ^c	Placebo (N=387) ^c	AUDENZ (N=1189) ^c	Placebo (N=397) ^c
Injection site pain	64	20	36	10
Erythema \geq 25 mm	0.6	0	0.4	0
Induration \geq 25 mm	0.4	0	0.7	0
Ecchymosis \geq 25 mm	0.3	0	0.6	0.3

^a NCT02839330

^b Severe (Grade 3) reactions of each type were reported in 1% or fewer subjects receiving AUDENZ; severe (Grade 3) reactions of each type were also reported in the placebo group at similar percentages. Grade 3 local pain is that which prevents daily activity; Grade 3 injection site erythema, induration and ecchymosis include any \geq 100 mm in diameter.

^c Number of subjects in the Solicited Safety Population (subjects who were vaccinated and provided any solicited safety data, excluding the 30-minute post-vaccination observation period) for each dose group.

Table 2: Percentages of Subjects 18 through 64 Years of Age and 65 Years of Age and Older Reporting Solicited Systemic Adverse Reactions within 7 Days after Any Vaccination with AUDENZ or Saline Placebo (Study 3^a).

Solicited Systemic Adverse Reactions ^b (%)	Adults 18 through 64 years of age	Adults 18 through 64 years of age	Adults 65 years of age and older	Adults 65 years of age and older
	AUDENZ (N=1163) ^c	Placebo (N=387) ^c	AUDENZ (N=1189) ^c	Placebo (N=397) ^c
Fatigue	25	21	20	19
Headache	25	23	16	16
Malaise	22	12	16	12
Myalgia	14	11	9	8
Arthralgia	10	9	10	9
Nausea	10	11	7	6
Loss of appetite	8	9	6	6
Chills	4	4	4	3
Fever (\geq 100.4°F)	0.6	2	0.7	0.3

^a NCT02839330

^b Severe (Grade 3) reactions of each type were reported in 1% or fewer subjects receiving AUDENZ; severe (Grade 3) reactions of each type were also reported in the placebo group at similar percentages. Grade 3 fever is any oral temperature \geq 102.2°F; for other systemic reactions, Grade 3 is that which prevents daily activity or leads to decreased oral intake.

^c Number of subjects in the Solicited Safety Population (subjects who were vaccinated and provided any solicited safety data, excluding the 30-minute post-vaccination observation period) for each dose group.

Unsolicited Adverse Events:

In Study 3, the proportion of subjects 18 years of age and older who reported unsolicited AEs in the 21 days after each vaccination was similar between AUDENZ and placebo groups (23% vs. 22%). The frequencies and types of unsolicited adverse events were similar between treatment groups. Across both age and treatment groups, most events were mild to moderate in severity and considered unrelated to vaccinations.

Serious Adverse Events (SAEs)

In Study 3, fatal and non-fatal SAEs reported in the 12 months following vaccinations among adults 18 through 64 years of age occurred in 2.9% of subjects who received AUDENZ and 3.3% of subjects who received placebo. SAE rates among adults 65 years of age and older were 10.5% in subjects administered AUDENZ and 15.3% in subjects who received placebo. Fatal SAEs included 11 (0.5%) AUDENZ recipients and 1 (0.1%) placebo recipients. No SAEs were assessed as being related to AUDENZ.

Studies 1 and 2 did not have a placebo or active comparator control for comparison of safety. Four deaths occurred in Study 1 (subjects 18 through 64 years) and two in Study 2 (subjects \geq 65 years), none assessed as related to AUDENZ. In the 12 months following vaccinations, SAEs (fatal and non-fatal) occurred in a total of n=28 (3%) of all subjects in Study 1. SAEs occurred in a total of n=96 (7%) subjects in Study 2. In both Studies 1 and 2, all SAEs appeared unrelated to study treatment.

Adverse Events of Special Interest (AESIs)

In Studies 1, 2, and 3 combined, AESIs, such as new onset neuroinflammatory and immune mediated diseases, were assessed in the studies using a predefined list. The percentages of subjects with an AESI at any time after vaccination was 0.2% among adults 18 through 64 years of age and 0.4% among adults 65 years of age and older who received AUDENZ. In the placebo group, 1.8% of adults 65 years and older reported AESIs while there were no AESIs reported for adults 18 through 64 years. No AESIs were assessed as related to AUDENZ.

New Onset of Chronic Diseases and Medically-Attended Adverse Events

In Studies 1, 2 and 3 combined, NOCDs (9.7% vs 9.2%) and MAAEs (47.1% vs 46.0%) occurred with similar frequencies between AUDENZ and placebo recipients, respectively, with larger proportions of these events occurring in subjects \geq 65 years. No large imbalances in types of events were observed between treatment groups.

Children and adolescents 6 months through 17 years of age:

Clinical safety data for AUDENZ in children 6 months through 17 years of age were collected in Study 4.

Study 4 was an observer-blind, multicenter study conducted in the U.S. and Thailand in children 6 months through 17 years of age (NCT01776554). A total of 329 subjects in the safety population received two doses of AUDENZ administered intramuscularly 21 days apart.

Solicited local (injection site) and systemic adverse reactions were collected for seven days (the

day of vaccination and for six days thereafter) following each vaccination in all children, divided into two age cohorts (6 months through 5 years [N=160], and 6 years through 17 years of age [N=163]). Unsolicited adverse events were collected for 21 days following each vaccination for children 6 months through 17 years of age. SAEs, AESIs, NOCDs, and MAAEs were monitored for one year after the last vaccination.

The mean age of subjects in Study 4 was 79 months (6.5 years), 54% were male, 72% were Asian, 22% white, 4% black or African American, 2% other, <1% American Indian or Alaska native, and 96% were non-Hispanic/non-Latino. A total of 72% of the safety population was enrolled in Thailand and 28% in the U.S.

Solicited Reactions:

The majority of solicited local and systemic adverse reactions reported in each age group of children 6 months through 5 years and 6 years through 17 years were mild or moderate in intensity, and resolved within a few days. The proportions of subjects who reported solicited local or systemic reactions were lower following the second vaccination as compared to the first.

The most common ($\geq 10\%$) solicited local and systemic reactions within 7 days following administration of AUDENZ in children 6 months through 5 years of age were tenderness (56%), irritability (30%), sleepiness (25%), change in eating habits (18%) and fever (16%). The most common ($\geq 10\%$) solicited local and systemic reactions within 7 days following administration of AUDENZ in children 6 years through 17 years of age were pain (68%), myalgia (30%), fatigue (27%), malaise (25%), headache (22%), loss of appetite (14%), nausea (13%), and arthralgia (13%).

The proportions of children 6 months through 5 years who reported solicited adverse reactions are presented in Tables 3 and 4.

Table 3: Percentage of Children 6 Months through 5 Years of Age with Solicited Adverse Local Reactions within 7 days after Any Vaccination with AUDENZ (Study 4^a)

Solicited Local Adverse Reactions^b	AUDENZ (N=159)^c %
Tenderness (Any)	56
Tenderness (Severe)	1
Erythema (≥ 10 mm)	3
Erythema (≥ 50 mm)	0
Induration (≥ 10 mm)	1
Induration (≥ 50 mm)	0
Ecchymosis (≥ 10 mm)	0
Ecchymosis (≥ 50 mm)	0

^a NCT01776554

^b Any erythema, induration or ecchymosis were defined as a measured diameter ≥ 10 mm. Severe (Grade 3) reactions were defined as follows: Tenderness = cried when injected limb was moved; Erythema, Induration and Ecchymosis = diameter ≥ 50 mm.

^c N = number of subjects in the Solicited Safety Population who were vaccinated and provided solicited local adverse event safety data, excluding the 30-minute post-vaccination observation period).

Table 4: Percentage of Children 6 Months through 5 Years of Age with Solicited Adverse Systemic Reactions within 7 days after Any Vaccination with AUDENZ (Study 4^a)

Solicited Systemic Adverse Reactions^b	AUDENZ (N=159-160)^c %
Irritability (Any)	30
Irritability (Severe)	1
Sleepiness (Any)	25
Sleepiness (Severe)	0
Change in eating habits (Any)	18
Change in eating habits (Severe)	0
Fever ($\geq 100.4^\circ$ F)	16
Fever ($\geq 102.1^\circ$ F)	2

^a NCT01776554

^b Severe (Grade 3) reactions were defined as follows: Irritability = unable to console; Sleepiness = sleeps most of the time and it is hard to arouse him/her; Change in eating habits = missed more than 2 feeds; Fever = body temperature $\geq 102.1^\circ$ F.

^c N = number of subjects in the Solicited Safety Population who were vaccinated and provided solicited systemic adverse event safety data, excluding the 30-minute post-vaccination observation period).

The reported frequencies of solicited adverse reactions in children 6 years through 17 years of age are presented in Tables 5 and 6.

Table 5: Percentage of Children 6 through 17 Years of Age with Solicited Local Adverse Reactions within 7 days after Any Vaccination with AUDENZ (Study 4^a)

Solicited Local Adverse Reactions^b	AUDENZ (N=163)^c %
Injection site pain (Any)	68
Injection site pain (Severe)	1
Erythema (≥ 25 mm)	1
Erythema (≥ 100 mm)	0
Induration (≥ 25 mm)	2
Induration (≥ 100 mm)	0
Ecchymosis (≥ 25 mm)	0
Ecchymosis (≥ 100 mm)	0

^a NCT01776554

^b Severe (Grade 3) reactions were defined as follows: Pain = prevented daily activity; Erythema, Induration and Ecchymosis = diameter > 100 mm; .

^c Number of subjects in the Solicited Safety Population who were vaccinated and provided solicited local adverse event safety data, excluding the 30-minute post-vaccination observation period).

Table 6: Percentage of Children 6 through 17 Years of Age with Solicited Systemic Adverse Reactions within 7 days after Any Vaccination with AUDENZ (Study 4^a)

Solicited Systemic Adverse Reactions ^b	AUDENZ (N=162-163) ^c %
Myalgia (Any)	30
Myalgia (Severe)	0
Fatigue (Any)	27
Fatigue (Severe)	1
Malaise (Any)	25
Malaise (Severe)	1
Headache (Any)	22
Headache (Severe)	0
Loss of appetite (Any)	14
Loss of appetite (Severe)	1
Nausea (Any)	13
Nausea (Severe)	1
Arthralgia (Any)	13
Arthralgia (Severe)	0
Fever ($\geq 100.4^{\circ}\text{F}$)	4
Fever ($\geq 102.1^{\circ}\text{F}$)	1

^a NCT01776554

^b Severe (Grade 3) reactions were defined as follows: Myalgia, Fatigue, Malaise, Headache, Nausea and Arthralgia = Prevents daily activity; Loss of appetite = Decreased oral intake with weight loss.

^c Number of subjects in the Solicited Safety Population who were vaccinated and provided solicited systemic adverse event safety data, excluding the 30-minute post-vaccination observation period).

Unsolicited Adverse Events:

In children 6 months through 17 years of age (N=329), 26% of subjects who received AUDENZ reported at least one unsolicited adverse event within 21 days after any vaccination. The most common unsolicited AEs ($\geq 2\%$) among all subjects were upper respiratory infection (8%), pyrexia (5%), nasopharyngitis (4%) and vomiting (2%). Most AEs were mild or moderate in severity. One child was discontinued from the second vaccination due to a non-serious AE (pyrexia on Day 3) assessed as possibly related to study vaccine.

Serious Adverse Events

A total of 8 (2%) children 6 months through 17 years of age in the safety population (N=326) experienced SAEs during the study. SAEs consisted of events typical for a pediatric population and were assessed as unrelated to study vaccine. No deaths were reported during the study.

Adverse Events of Special Interest

No AESIs were reported during the study.

New Onset of Chronic Diseases and Medically-Attended Adverse Events

No AUDENZ recipients reported NOCDs during the study. MAAEs were reported by 34% of all subjects and were typical of events that occur in a pediatric population. The most common MAAEs were categorized as infections and infestations (reported by 26% of subjects).

6.2 Postmarketing Experience

There is no postmarketing experience following administration of AUDENZ.

The following adverse events have been reported during postmarketing use of influenza vaccines that contain the same MF59[®] adjuvant or share the same manufacturing platform as the influenza antigen in AUDENZ.

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.

Blood and lymphatic system disorders: Lymphadenopathy.

Immune system disorders: Hypersensitivity reactions including angioedema and anaphylaxis.

Nervous system disorders: Bell's Palsy, convulsions, including febrile convulsion, demyelination, encephalitis, Guillain-Barré Syndrome, neuritis, paresthesia, syncope.

Skin and subcutaneous tissue disorders: Urticaria, pruritis, non-specific rash.

Musculoskeletal and connective tissue disorders: Muscular weakness.

7 DRUG INTERACTIONS

7.1 Concomitant Vaccine Administrations

No data are available to evaluate the concomitant administration of AUDENZ with other vaccines.

7.2 Concurrent Use with Immunosuppressive Therapies

Immunosuppressive or corticosteroid therapies may reduce the immune response to AUDENZ.

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 U.S. 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 insufficient data on AUDENZ in pregnant women to inform vaccine-associated risks in pregnancy.

A developmental toxicity study was performed in female rabbits administered AUDENZ prior to mating and during gestation. A 0.5 mL dose was injected on each occasion (a single human dose is 0.5 mL). This study revealed no evidence of harm to the fetus or offspring due to AUDENZ [see 8.1 Data].

Clinical Considerations

Disease-associated Maternal and/or Embryo/Fetal Risk

There is limited information on the risk of influenza A (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

In a developmental toxicity study, female rabbits were administered 0.5 mL of AUDENZ by intramuscular injection 1 and 3 weeks prior to mating, and on gestation days 7 and 20. No vaccine-related fetal malformations or variations and no adverse effects on pre-weaning development were observed in the study.

8.2 Lactation

Risk Summary

It is not known whether AUDENZ is excreted in human milk. Data are not available to assess the effects of AUDENZ 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 AUDENZ and any potential adverse effects on the breastfed child from AUDENZ 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 AUDENZ in infants younger than 6 months have not been established.

8.5 Geriatric Use

Two clinical studies of AUDENZ included a total of 1,896 subjects 65 years of age and older administered AUDENZ. Of these, 533 subjects were 75 years of age and older.

Subjects 65 years of age and older had a lower immune response to AUDENZ than subjects 18 through 64 years; the pre-specified targets for the immunogenicity endpoints were met in the geriatric subjects [*see Clinical Studies (14)*]. No clinically relevant differences in safety between subjects 65 years of age and older and younger subjects were observed [*see Adverse Reactions (6)*].

11 DESCRIPTION

AUDENZ, a sterile injectable emulsion for intramuscular use, is an inactivated, monovalent, subunit influenza vaccine prepared from virus propagated in Madin Darby Canine Kidney (MDCK) cells, a continuous cell line. These cells were adapted to grow freely in suspension in culture medium. The virus is inactivated with β -propiolactone, disrupted by the detergent cetyltrimethylammonium bromide and purified through several process steps. The influenza antigen contained in AUDENZ is manufactured according to the same process as that used to produce the antigens contained in FLUCELVAX[®] and FLUCELVAX[®] QUADRIVALENT, which are unadjuvanted seasonal influenza vaccines licensed for use in the United States.

AUDENZ is a milky-white emulsion. Each 0.5 mL dose is formulated to contain 7.5 mcg of hemagglutinin (HA) of the influenza virus strain A/turkey/Turkey/1/2005 NIBRG-23, a reverse genetics-derived reference strain supplied by the National Institute for Biological Standards and Control (NIBSC), and MF59C.1 adjuvant (MF59), a squalene-based oil-in-water emulsion (9.75 mg squalene, 1.175 mg polysorbate 80, 1.175 mg sorbitan trioleate, 0.66 mg sodium citrate dihydrate and 0.04 mg citric acid monohydrate), at pH 6.5-7.7.

Each dose of AUDENZ may also contain residual amounts of protein other than HA (≤ 30 mcg) including MDCK cell protein (≤ 3.15 mcg), MDCK cell DNA (≤ 10 ng), additional polysorbate 80 (≤ 0.375 mg), cetyltrimethylammonium bromide (≤ 4.5 mcg), and β -propiolactone (≤ 0.1 mcg), which are used in the manufacturing process.

AUDENZ contains no antibiotics.

AUDENZ 0.5 mL single-dose pre-filled syringes contain no preservative.

AUDENZ 5 mL multi-dose vials contain thimerosal, a mercury derivative, added as a preservative. Each 0.5 mL dose from the multi-dose vial contains 25 mcg mercury.

The tip caps and plungers of the pre-filled syringes and the multi-dose vial stopper 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 virus strains, antibody titers of $\geq 1:40$ have been associated with protection from influenza illness in up to 50% of subjects [*see References (2, 3)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

AUDENZ has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility in animals. Administration of AUDENZ did not affect female fertility in a rabbit developmental toxicity study [*see Pregnancy (8.1)*].

14 CLINICAL STUDIES

The influenza antigen contained in AUDENZ is manufactured according to the same process as that used to produce the antigens contained in FLUCELVAX and FLUCELVAX QUADRIVALENT, which are unadjuvanted seasonal influenza vaccines licensed in the United States. Effectiveness of AUDENZ was demonstrated based on serum HI antibody responses to AUDENZ and effectiveness of FLUCELVAX, including a demonstration of efficacy of FLUCELVAX in the prevention of influenza disease in adults 18 through 49 years of age, and in children and adolescents 2 years through 17 years of age, and demonstration of non-inferior immunogenicity of Flucelvax as compared to a U.S.-licensed comparator inactivated quadrivalent influenza vaccine in children 6 through 23 months.

14.1 Immunological Evaluation

Adults 18 years of age and older:

Study 3 was a phase 3, randomized, observer-blind, multicenter, placebo-controlled trial conducted in the United States in 3,196 adults 18 years of age and older, who were stratified by age and randomized 3:1 to receive either two doses of AUDENZ or saline placebo, 21 days apart. The mean age of all enrolled subjects was 58 years, 55% were female, 84% were white, 13% black or African American, 1% Asian, and 92% non-Hispanic/non-Latino. In total, 2,988 subjects (18 through 64 years N=1,488; ≥ 65 years N=1,500) in the per protocol population received both doses of AUDENZ (N=2,249) or placebo (N=739). HI antibody titers against the A/turkey/Turkey/1/2005 (H5N1) strain were evaluated in sera obtained 21 days after the second dose.

HI titers were assessed according to prespecified criteria for the proportion of subjects with seroconversion (defined as a pre-vaccination HI titer $< 1:10$ and post-vaccination HI titer $\geq 1:40$ or a pre-vaccination HI titer $\geq 1:10$ and ≥ 4 -fold increase in HI titer) and the proportion of subjects with a post-vaccination HI titer $\geq 1:40$. Assessment of the proportion of subjects with seroconversion or an HI titer $\geq 1:40$ after vaccination was assessed by age group (18 through 64 years and ≥ 65 years). Success criteria required the lower bound of the 2-sided 95% CI for the proportion of subjects with seroconversion, to be $\geq 40\%$ for subjects 18 through 64 years, and $\geq 30\%$ for subjects ≥ 65 years of age. For the proportion of subjects with an HI titer $\geq 1:40$, the lower bound of the 2-sided 95% CI was required to be $\geq 70\%$ for subjects 18 through 64 years of age, and $\geq 60\%$ for subjects ≥ 65 years of age.

In subjects 18 through 64 years of age and in subjects ≥ 65 years of age, the prespecified criteria for proportion of subjects with seroconversion and an HI titer $\geq 1:40$ were met 21 days after the second vaccination (Table 7).

Table 7. Seroconversion Rates and Percentage of Subjects with HI Titers $\geq 1:40$ following AUDENZ or Placebo (21 Days after Second Dose) by Age Cohort – Per Protocol Set^a (Study 3^b)

Immune Response	Adults 18 through 64 years of age	Adults 18 through 64 years of age	Adults 65 years of age and older	Adults 65 years of age and older
	AUDENZ (N=1076)	Placebo (N=349)	AUDENZ (N=1080)	Placebo (N=351)
% Seroconversion ^c (95% CI)	79.9% (77.4, 82.3)	0.3% (0.0, 1.6)	54.0% (51.0, 57.0)	1.7% (0.6, 3.7)
% HI Titer $\geq 1:40$ ^d (95% CI)	95.0% (93.4, 96.2)	8.5% (5.9, 12.1)	85.7% (83.3, 87.9)	20.8% (16.6, 25.8)

Abbreviations: N=number of subjects in each group, Per Protocol Set; HI=hemagglutinin inhibition; CI=confidence interval.

^a Per Protocol Set: subjects who received 2 doses of AUDENZ according to the study protocol

^b ClinicalTrials.gov identifier: NCT02839330

^c Seroconversion is defined as a pre-vaccination HI titer $< 1:10$ and post-vaccination HI titer $\geq 1:40$ or a pre-vaccination HI titer $\geq 1:10$ and ≥ 4 -fold increase in HI titer. Success criteria for seroconversion: For subjects 18 to < 65 years, the lower bound (LB) of the 95% CI for the Seroconversion must be $\geq 40\%$; for subjects ≥ 65 years, the LB of the 95% CI for the Seroconversion must be $\geq 30\%$.

^d %HI titer $\geq 1:40$ is the percentage of subjects with an HI titer of at least 1:40 at 21 days following the second vaccination. Success criteria for %HI $\geq 1:40$: For subjects 18 to < 65 years, the lower bound (LB) of the 95% CI for the % HI ≥ 40 must be $\geq 70\%$; for subjects ≥ 65 years, the LB of the 95% CI for the % HI ≥ 40 must be $\geq 60\%$.

Children and adolescents 6 months through 17 years of age:

Study 4 was an observer-blind multicenter study conducted in Thailand and the U.S. in children 6 months through 17 years of age, stratified by age (6 through 35 months, 3 through 8 years, and 9 through 17 years). A total of 289 subjects in the full analysis population received two doses of AUDENZ, 21 days apart.

The mean age of the subjects was 79.6 months; 55% of the subjects were male, 72% of the participants were Asian, 23% were White, and 3% were Black or African American, and 96% were non-Hispanic/non-Latino. A total of 72% of subjects were from Thailand and 28% from the U.S. HI antibody titers against the A/turkey/Turkey/1/2005 (H5N1) strain were evaluated in sera obtained 21 days after the second dose in the overall full analysis population and in the three age cohorts.

The co-primary endpoints for the overall full analysis population were: 1) the proportion of subjects with seroconversion and 2) the proportion of subjects with an HI titer of $\geq 1:40$ after

vaccination, each were evaluated according to prespecified criteria. Success criteria applied to the co-primary endpoint analyses were as follows: 1) for the proportion of subjects with seroconversion (defined as a pre-vaccination HI titer <1:10 and post-vaccination HI titer \geq 1:40, or a pre-vaccination HI titer \geq 1:10 and \geq 4-fold increase in HI titer), the lower bound of the 2-sided 97.5% CI should be \geq 40%; and 2) for the proportion of subjects with an HI titer \geq 1:40, the lower bound of the 2-sided 97.5% CI should be \geq 70%. Similar criteria, using 95% CIs, were applied to secondary analyses of each age subgroup.

In both the overall full analysis population and in all three age subgroups, the prespecified criteria for the proportions of subjects with seroconversion and an HI titer \geq 1:40 were met at 21 days after the second vaccination with AUDENZ. These data are presented in Table 8.

Table 8. Seroconversion Rates and Percentage of Subjects with HI Titers \geq 1:40 at 21 days following the second dose of AUDENZ – Full Analysis Set^a (Study 4^b)

Immune Response	Overall Population	Age Subgroup	Age Subgroup	Age Subgroup
	6 months through 17 years (N=279 – 287)	6 months through 35 months (N= 84 – 91)	3 years through 8 years (N= 93 – 94)	9 years through 17 years (N= 102)
% Seroconversion ^c (97.5% CI, overall) (95% CI, subgroups)	96% (93, 98)	99% (94, 100)	98% (92, 100)	92% (85, 97)
% HI Titer \geq 1:40 ^d (97.5% CI, overall) (95% CI subgroups)	96% (92, 98)	98% (92, 100)	98% (93, 100)	92% (85, 97)

Abbreviations: HI=hemagglutinin inhibition; CI=confidence interval; N=number of subjects in the FAS at the Day 43 timepoint.

^a FAS: Full Analysis Set, subjects who received at least one dose of AUDENZ and provided immunogenicity data at the relevant timepoints, i.e. at Days 1 and 43 for the primary analysis.

^b ClinicalTrials.gov identifier: NCT01776554.

^c Seroconversion is defined as a prevaccination HI titer < 1:10 and postvaccination HI titer \geq 1:40 or a prevaccination HI titer \geq 1:10 and \geq 4-fold increase in HI titer. Success criteria for seroconversion: For subjects 6 months through 17 years overall, the lower bound (LB) of the 97.5% CI for the seroconversion rate (SCR) must be \geq 40%; for each age subgroup, the LB of the 95% CI for the SCR must be \geq 40%.

^d %HI titer \geq 1:40 is the percentage of subjects with an HI titer of at least 1:40. Success criteria for the %HI \geq 1:40: For subjects 6 months through 17 years, the lower bound (LB) of the 97.5% CI for the % HI \geq 40 must be \geq 70%; For each age subgroup, the lower bound (LB) of the 95% CI for the % HI \geq 40 must be \geq 70%

15 REFERENCES

1. Lasky T, Terracciano GJ, Magder L, et al. The Guillain-Barre syndrome and the 1992-1993 and 1993-1994 influenza vaccines. *N Engl J Med* 1998; 339 (25): 1797-1802.
2. Hannoun C, Megas F, Piercy J. Immunogenicity and protective efficacy of influenza vaccination. *Virus Res* 2004; 103:133-138.

3. Hobson D, Curry RL, Beare A, et al. The role of serum hemagglutinin-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. *J Hyg Camb* 1972;767-777.

16 HOW SUPPLIED/STORAGE AND HANDLING

Information on the AUDENZ package presentation is provided in Table 9 below.

Table 9. AUDENZ Product Presentations

Presentation	Package size	Carton NDC Number	Description of Component and Component NDC Number
Pre-filled Syringe	10 syringes per carton	70461-700-03	0.5 mL single dose pre-filled syringe [NDC 70461-700-04]
Multi-dose Vial	25 vials per carton	70461-800-40	5 mL multi-dose vial [NDC 70461-800-41]

The tip caps and plungers of the pre-filled syringes and the multi-dose vial stopper are not made with natural rubber latex.

AUDENZ should be stored in a refrigerator at 2°C to 8°C (36°F to 46°F). **Do not freeze.** Do not use if previously frozen. Protect from light.

17 PATIENT COUNSELING INFORMATION

- Emphasize that it is important to complete the two-dose immunization series.
- Inform vaccine recipients, parents or guardians of the potential benefits and risks of immunization with AUDENZ.
- Educate vaccine recipients, parents or guardians of potential side effects and instruct them to report any adverse events to their healthcare provider and/or VAERs at 1-800-822-7967 or www.vaers.hhs.gov.
- Inform vaccine recipients, parents or guardians that AUDENZ contains non-infectious particles and cannot cause influenza.
- Inform vaccine recipients, parents or guardians that AUDENZ is intended to provide protection against illness due to influenza virus contained in the vaccine.

Manufactured by: **Seqirus Inc.** 475 Green Oaks Parkway, Holly Springs, NC 27540, U.S.A.

U.S. License No. 2049

Distributed by: **Seqirus USA Inc.** 25 Deforest Avenue, Summit NJ 07901, U.S.A
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