**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all information needed to use ACAM2000 safely and effectively. See full prescribing information for ACAM2000.**

**ACAM2000, (Smallpox (Vaccinia) Vaccine, Live)**

**Lyophilized preparation for percutaneous scarification**

**Initial U.S. Approval: 2007**

**WARNING:**

*See full prescribing information for complete boxed warning*

- **Myocarditis and pericarditis (suspect cases observed at a rate of 5.7 per 1000 primary vaccinees (95% CI: 1.9-13.3)), encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia, generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including STEVENS-JOHNSON SYNDROME), eczema vaccinatum resulting in permanent sequelae or death, ocular complications, blindness and fetal death, have occurred following either primary vaccination or revaccination with live vaccinia virus smallpox vaccines. These risks are increased in certain individuals and may result in severe disability, permanent neurological sequelae and/or death [see Warnings and Precautions (5)].**

**----------INDICATIONS AND USAGE----------**

ACAM2000® is indicated for active immunization against smallpox disease for persons determined to be at high risk for smallpox infection.

**----------DOSAGE AND ADMINISTRATION----------**

- Administer ACAM2000 only after being trained on the safe and effective administration of the vaccine by the percutaneous route (scarification). (2.3)
- A droplet of ACAM2000 is administered by the percutaneous route (scarification) using 15 jabs of a bifurcated needle. ACAM2000 should not be injected by the intradermal, subcutaneous, intramuscular, or intravenous route. (2.3)
- The droplet (0.0025 mL) of reconstituted vaccine is picked up with a bifurcated needle by dipping needle into ACAM2000 vial. (2.3)
- See full prescribing information for instructions for vaccine preparation (2.2), administration including provision of the Medication Guide to vaccinees and instruction to vaccinees about vaccination site care, (2.3) and interpretation of response to vaccination. (2.4)
- Re-vaccination may be recommended (e.g. every 3 years). (2.5)

**----------DOSAGE FORMS AND STRENGTHS----------**

- Lyophilized powder reconstituted with packaged diluent. After reconstitution, each vial has approximately 100 doses of 0.0025 mL of live vaccinia virus containing 2.5 – 12.5 x $10^5$ plaque forming units. (3)

**----------CONTRAINDICATIONS----------**

- Individuals with severe immunodeficiency who are not expected to benefit from the vaccine. These individuals may include persons who are undergoing bone marrow transplantation or persons with primary or acquired immunodeficiency states who require isolation (4).

**-- ----------WARNINGS AND PRECAUTIONS----------**

- Myocarditis and/or pericarditis, ischemic heart disease and non-ischemic dilated cardiomyopathy. (5.1, 5.2)
- Encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia (vaccinia necrosum), generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including Stevens-Johnson syndrome), eczema vaccinatum, fetal vaccinia and fetal death. (5.1)
- Ocular vaccinia and blindness. (5.3)
- These risks, including risks of severe disability and/or death, are increased in vaccinees with:
  - Cardiac disease (5.2).
  - Eye disease treated with topical steroids. (5.3)
  - Congenital or acquired immune deficiency disorders. (5.4)
  - History or presence of eczema and other skin conditions. (5.5)
  - Infants < 12 months of age. (5.6)
  - Pregnancy (5.7)
- ACAM2000 is a live vaccinia virus that can be transmitted to persons who have close contact with the vaccinee and the risks in contacts are the same as those stated for vaccinees. (5.10)

**----------ADVERSE REACTIONS----------**

Common adverse events include inoculation site signs and symptoms, lymphadenitis, and constitutional symptoms, such as malaise, fatigue, fever, myalgia, and headache (6.1). These adverse events are less frequent in revaccinated persons than persons receiving the vaccine for the first time.

Inadvertent inoculation at other sites is the most frequent complication of vaccinia vaccination. The most common sites involved are the face, nose, mouth, lips, genitalia and anus.

Self-limited skin rashes not associated with vaccinia replication in skin, including urticaria and folliculitis, may occur following vaccination.

**To report SUSPECTED ADVERSE REACTIONS, contact Sanofi Pasteur. at 1-800-822-2463 (1-800-VACCINE) or VAERS at 800-822-7967 and https://vaers.hhs.gov.**

**----------USE IN SPECIFIC POPULATIONS----------**

- ACAM2000 may rarely cause fetal infection, usually resulting in stillbirth or death. (8.1)
- ACAM2000 live vaccinia virus may be transmitted from a lactating mother to her infant causing complications in the infant from inadvertent inoculation. (8.3)
- ACAM2000 may be associated with an increased risk of serious complications in children, especially in infants younger than 12 months. (8.4)

**See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE**

**Revised: [01/2015]**

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**FULL PRESCRIBING INFORMATION**

**WARNING:**

- Suspected cases of myocarditis and/or pericarditis have been observed in healthy adult primary vaccinees (at an approximate rate of 5.7 per 1000, 95% CI: 1.9-13.3) receiving ACAM2000 [see Warnings and Precautions (5.1)].
- Encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia, generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including STEVENS-JOHNSON SYNDROME), eczema vaccinatum resulting in permanent sequelae or death, ocular complications, blindness, and fetal death have occurred following either primary vaccination or revaccination with live vaccinia virus smallpox vaccines [see Warnings and Precautions (5)].

  These risks are increased in vaccinees with the following conditions and may result in severe disability, permanent neurological sequelae and/or death:
  - Cardiac disease or a history of cardiac disease
  - Eye disease treated with topical steroids
  - Congenital or acquired immune deficiency disorders, including those taking immunosuppressive medications
  - Eczema and persons with a history of eczema or other acute or chronic exfoliative skin conditions
  - Infants less than 12 months of age
  - Pregnancy

ACAM2000 is a live vaccinia virus that can be transmitted to persons who have close contact with the vaccinee and the risks in contacts are the same as those for the vaccinee.

The risk for experiencing serious vaccination complications must be weighed against the risks for experiencing a potentially fatal smallpox infection.

## 1 INDICATIONS AND USAGE

ACAM2000® is indicated for active immunization against smallpox disease for persons determined to be at high risk for smallpox infection.

## 2 DOSAGE AND ADMINISTRATION

Administer ACAM2000 only after being trained on the safe and effective administration of the vaccine by the percutaneous route (scarification). ACAM2000 should not be injected by the intradermal, subcutaneous, intramuscular, or intravenous route. Provide each patient with the FDA-approved Medication Guide prior to administering the vaccine.

### 2.1 Instructions for Vaccine Preparation

#### 2.1.1 Reconstitution

ACAM2000 is reconstituted by addition of 0.3 mL of diluent to the vial containing lyophilized vaccine. **Note: this 0.3 mL of diluent is not the entire content of the diluent vial.** ACAM2000 should only be reconstituted with 0.3 mL of the diluent provided. The vaccine vial should be removed from cold storage and brought to room temperature before reconstitution. The flip cap seals of the vaccine and diluent vials are removed, and each rubber stopper is wiped with an isopropyl alcohol swab and allowed to dry thoroughly. Using aseptic technique and a sterile 1 mL syringe fitted with a 25 gauge x 5/8" needle (provided), draw up 0.3 mL of diluent and transfer the entire content of the syringe to the vaccine vial. Gently swirl to mix but try not to get product on the rubber stopper. The reconstituted vaccine should be a clear to slightly hazy, colorless to straw-colored liquid free from extraneous matter. Reconstituted vaccine should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter or discoloration is observed, the vaccine should not be used and the vial should be disposed safely. [See Preparation / Handling Precautions and Instructions for Disposal (2.2)]

#### 2.1.2 Storage following Reconstitution

After reconstitution, ACAM2000 vaccine may be administered within 6 to 8 hours if kept at room temperature (20-25°C, 68-77°F). Unused, reconstituted ACAM2000 vaccine may be stored in a refrigerator (2-8°C, 36-46°F) up to 30 days, after which it should be discarded as a biohazardous material. [See Preparation / Handling Precautions and Instructions for Disposal (2.2)] Exposure of reconstituted vaccine to room temperature during vaccination sessions should be minimized by placing it in refrigerator or on ice between patient administrations.

### 2.2 Preparation / Handling Precautions and Instructions for Disposal

Personnel preparing and administering the vaccine should wear surgical or protective gloves and avoid contact of vaccine with skin, eyes or mucous membranes.

The vaccine vial, its stopper, the diluent syringe, the vented needle used for reconstitution, the bifurcated needle used for administration, and any gauze or cotton that came in contact with the vaccine should be discarded in leak-proof, puncture-proof biohazard containers. These containers should then be disposed of appropriately.

### 2.3 Vaccination Instructions

The site of vaccination is the upper arm over the insertion of the deltoid muscle.

No skin preparation should be performed unless the skin at the intended site of vaccination is obviously dirty, in which case an alcohol swab(s) may be used to clean the area. If alcohol is used, the skin must be allowed to dry thoroughly to prevent inactivation of the live vaccine virus by the alcohol.

Remove the vaccine vial cap. Remove bifurcated needle from individual wrapping. Submerge bifurcated end of needle in reconstituted vaccine solution. The needle will pick up a droplet of vaccine (0.0025 mL) within the fork of the bifurcation. Use aseptic technique, i.e., do not insert the upper part of the needle that has been in contact with fingers into the vaccine vial, and never re-dip the needle into the vaccine vial if the needle has touched skin.

Deposit the droplet of vaccine onto clean, dry skin of the arm prepared for vaccination. The needle is held between thumb and first finger perpendicular to the skin. The wrist of the hand holding the needle of the vaccinator rests against the patient's arm. Rapidly make 15 jabs of the needle perpendicular to the skin through the vaccine droplet to puncture the skin, within a diameter of about 5 mm. The jabs should be vigorous enough so that a drop of blood appears at the vaccination site.

Any excess droplets of vaccine and blood should be wiped off the skin using a dry gauze pad and discarded in a biohazard container. Discard the needle in a biohazard sharps container. Close the vaccine vial by reinserting the rubber cap and return to a refrigerator or place on ice unless it will be used immediately to vaccinate another subject. [See Storage Following Reconstitution (2.1.2)]

Cover the vaccination site loosely with a gauze bandage, using first aid adhesive tape to keep it in place. This bandage provides a barrier to protect against spread of the vaccinia virus. If the vaccinee is involved in direct patient care, the gauze should be covered with a semipermeable (semiocclusive) dressing as an additional barrier. A semipermeable dressing is one that allows for the passage of air but does not allow for the passage of fluids.

Wash hands with soap and warm water or with alcohol-based hand rubs such as gels or foams after direct contact with the vaccination site, the bandage or clothes, towels or sheets that might be contaminated with virus from the vaccination site. This is vital in order to remove any virus from your hands and prevent contact spread.

Put the contaminated bandages in a sealed plastic bag and throw them away in the trash.

Wash separately clothing, towels, bedding or other items that may have come in direct contact with the vaccination site or drainage from the site, using hot water with detergent and/or bleach. Wash hands afterwards.

Don't use a bandage that blocks air from the vaccination site. This may cause the skin at the vaccination site to soften and wear away. Use loose gauze secured with medical tape to cover the site.

Don't put salves or ointments on the vaccination site.

### 2.4 Instructions for Interpreting Vaccination Response

#### 2.4.1 Primary Vaccinees

In an individual vaccinated for the first time (primary vaccination), the expected response to vaccination is the development of a major cutaneous reaction (characterized by a pustule) at the site of inoculation. The lesion evolves gradually, with appearance of a papule at the site of vaccination after 2-5 days. The papule becomes vesicular, then pustular, and reaches its maximum size at 8-10 days after vaccination. The pustule dries and forms a scab, which usually separates within 14-21 days, leaving a pitted scar. (See Figure 1) Formation of a major cutaneous reaction by day 6-8 is evidence of a successful 'take' and acquisition of protective immunity. An equivocal reaction is any reaction that is not a major reaction, and indicates a non-take (vaccination failure) due to impotent vaccine or inadequate vaccination technique.

#### 2.4.2 Previously Vaccinated Individuals (Revaccination)

Successful vaccination in an individual previously exposed to vaccine is confirmed when a major cutaneous reaction [See Primary Vaccinees (2.4.1) and Figure 1] is observed 6 to 8 days post-vaccination. However any prior vaccination may modify (reduce) the cutaneous response upon revaccination (Figure 2) such that the absence of a cutaneous response does not necessarily indicate vaccination failure. Previously vaccinated individuals who do not have a cutaneous response on revaccination do not require revaccination to try to elicit a cutaneous response.

#### 2.4.3 Vaccination Failures

Individuals who are not successfully vaccinated (i.e., vaccination failures) after primary vaccination may be revaccinated again in an attempt to achieve a satisfactory take. The vaccination procedures should be checked, and vaccination repeated with vaccine from another vial or vaccine lot, employing the same technique described in 2.3 [See Vaccination Instructions (2.3)].

If a repeat vaccination is conducted using vaccine from another vial or vaccine lot fails to produce a major reaction, healthcare providers should consult the Centers for Disease Control and Prevention (CDC) at (404) 639-3670 or their state or local health department before giving another vaccination.

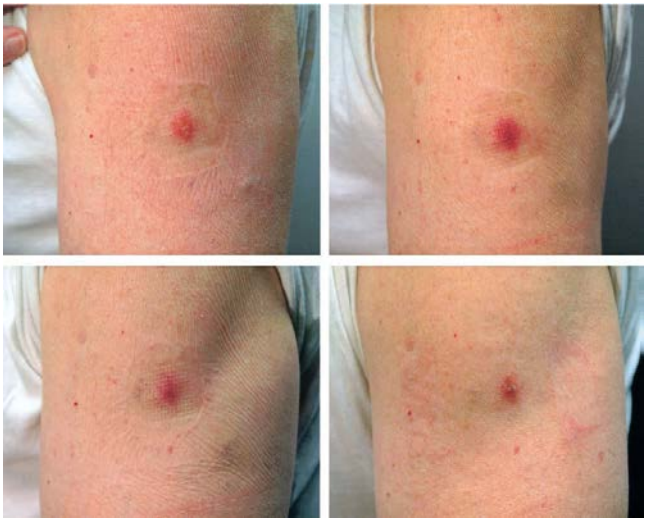
**Figure 1: Progression of major cutaneous reaction after primary vaccination[1]**

**Day 5** **Day 8**

**Day 10** **Day 14**

**Figure 2: Progression of major cutaneous reaction after revaccination[1]**

**Day 3** **Day 7**



**Day 10** **Day 14**

### 2.5 Booster Schedule

Persons at continued high risk of exposure to smallpox (e.g., research laboratory workers handling variola virus) should receive repeat ACAM2000 vaccination every three years.

### 2.6 Smallpox Vaccination Recommendations from US Government Agencies

Additional information may be obtained from U.S. Department of Defense (http://www.dtic.mil/whs/directives/corres/html/620503.htm) and U.S. Centers for Disease Control and Prevention (CDC) about smallpox vaccination (http://www.bt.cdc/gov/agent/smallpox/vaccination).

## 3 DOSAGE FORMS AND STRENGTHS

After reconstitution of the lyophilized preparation, each vial has approximately 100 doses of 0.0025 mL of vaccinia virus (live) containing 2.5-12.5x$10^5$ plaque forming units / dose.

## 4 CONTRAINDICATIONS

There are very few absolute contraindications to this vaccine for those who are at high risk for smallpox. The risk for experiencing serious vaccination complications must be weighed against the risks for experiencing a potentially fatal smallpox infection. See *Warnings and Precautions* (5) for persons who are at higher risk of experiencing serious vaccination complications.

**Severe Immune Deficiency**

Severe localized or systemic infection with vaccinia (progressive vaccinia) may occur in persons with weakened immune systems. Individuals with severe immunodeficiency who are not expected to benefit from the vaccine should not receive ACAM2000. These individuals may include individuals who are undergoing bone marrow transplantation or individuals with primary or acquired immunodeficiency who require isolation.

## 5 WARNINGS AND PRECAUTIONS

Persons at greatest risk of experiencing serious vaccination complications are often those at greatest risk for death from smallpox. The risk for experiencing serious vaccination complications must be weighed against the risks for experiencing a potentially fatal smallpox infection.

### 5.1 Serious Complications and Death

Serious complications that may follow either primary live vaccinia smallpox vaccination or revaccination include: myocarditis and/or pericarditis, encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia (vaccinia necrosum), generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including Stevens-Johnson syndrome), eczema vaccinatum, blindness, and fetal death in pregnant women. These complications may rarely lead to severe disability, permanent neurological sequelea and death. Based on clinical trials, symptoms of suspected myocarditis or pericarditis (such as chest pain, raised troponin/cardiac enzymes, or ECG abnormalities) occur in 5.7 per 1000 primary vaccinations. This finding includes cases of acute symptomatic or asymptomatic

myocarditis or pericarditits or both. Historically, death following vaccination with live vaccinia virus is a rare event; approximately 1 death per million primary vaccinations and 1 death per 4 million revaccinations have occurred after vaccination with live vaccinia virus. Death is most often the result of sudden cardiac death, postvaccinial encephalitis, progressive vaccinia, or eczema vaccinatum. Death has also been reported in unvaccinated contacts accidentally infected by individuals who have been vaccinated.

#### 5.1.1 Incidence of Serious Complications in 1968 US Surveillance Studies

Estimates of the risks of occurrence of serious complications after primary vaccination and revaccination, based on safety surveillance studies conducted when live vaccinia virus smallpox vaccine (i.e., New York City Board of Health strain, Dryvax®) was routinely recommended, are as follows:

**Table 1A - Rates of reported complications[(a)] associated with primary vaccinia vaccinations (cases/million vaccinations)[(b)]**

| Age (yrs) | <1 | 1-4 | 5-19 | ≥20 | Overall rates[(h)] |
|---|---|---|---|---|---|
| **Inadvertent inoculation[(c)]** § | 507.0 | 577.3 | 371.2 | 606.1 | **529.2** |
| **Generalized vaccinia** | 394.4 | 233.4 | 139.7 | 212.1 | **241.5** |
| **Eczema vaccinatum** | 14.1 | 44.2 | 34.9 | 30.3 | **38.5** |
| **Progressive vaccinia[(d)]** | --[(g)] | 3.2 | --[(g)] | --[(g)] | **1.5** |
| **Post-vaccinial encephalitis** | 42.3 | 9.5 | 8.7 | --[(g)] | **12.3** |
| **Death[(e)]** | 5 | 0.5 | 0.5 | unknown | -- |
| **Total[(f)]** | **1549.3** | **1261.8** | **855.9** | **1515.2** | **1253.8** |

[a] See article for descriptions of complications.
[b] Adapted from Lane JM, Ruber FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968: results of ten statewide surveys. J Infect Dis. 1970; 122:303-309.
[c] Referenced as accidental implantation.
[d] Referenced as vaccinia necrosum.
[e] Death from all complications.
[f] Rates of overall complications by age group include complications not provided in this table, including severe local reactions, bacterial superinfection of the vaccination site, and erythema multiforme.
[g] No instances of this complication were identified during the 1968 10-state survey.
[h] Overall rates for each complication include persons of unknown age.

**Table 1B - Rates of reported serious complications[(a)] associated with vaccinia revaccinations (cases/million vaccinations)[(b)]**

| Age (yrs) | <1 | 1-4 | 5-19 | ≥20 | Overall rates[(b)] |
|---|---|---|---|---|---|
| **Inadvertent inoculation[(c)]** | [(g)] | 109.1 | 47.7 | 25.0 | **42.1** |
| **Generalized vaccinia** | [(g)] | [(g)] | 9.9 | 9.1 | **9.0** |
| **Eczema vaccinatum** | [(g)] | [(g)] | 2.0 | 4.5 | **3.0** |
| **Progressive vaccinia[(d)]** | [(g)] | [(g)] | [(g)] | 6.8 | **3.0** |
| **Post-vaccinial encephalitis** | [(g)] | [(g)] | [(g)] | 4.5 | **2.0** |
| **Death[(e)]** | -- | -- | -- | -- | -- |
| **Total[(f)]** | [(g)] | **200.0** | **85.5** | **113.6** | **108.2** |

See Table 1A for explanation of footnotes.

#### 5.1.2 Incidence of Serious Complications and Emergence of Myocarditis and/or Pericarditis in 2002-2005

Data on the incidence of adverse events among U.S. military personnel and civilian first responders vaccinated with Dryvax®, a licensed live vaccinia virus smallpox vaccine, during vaccination programs initiated in December 2002 are shown below in Table 2. The incidence of preventable adverse events (eczema vaccinatum, contact transmission, and auto-inoculation) were notably lower in these programs when compared with data collected in the 1960s; presumably because of better vaccination screening procedures and routine use of protective bandages over the inoculation site. Myocarditis and pericarditis were not commonly reported following smallpox vaccination in the 1960s, but emerged as a more frequent event based on more active surveillance in the military and civilian programs.

**Table 2 - Serious adverse events in 2002-2005 [5]**

| Adverse event | Department of Defense program (n=730,580[a]) as of Jan05 | | Department of Health and Human Services program (n=40, 422) as of Jan04[b] | |
|---|---|---|---|---|
| | N | Incidence/ million | N | Incidence /million |
| **Myo/pericarditis** | 86 | 117.71 | 21 | 519.52 |
| **Post-vaccinal encephalitis** | 1 | 1.37 | 1 | 24.74 |
| **Eczema vaccinatum** | 0 | 0.00 | 0 | 0.00 |
| **Generalized vaccinia** | 43 | 58.86 | 3 | 74.22 |
| **Progressive vaccinia** | 0 | 0.00 | 0 | 0.00 |
| **Fetal vaccinia** | 0 | 0.00 | 0 | 0.00 |
| **Contact transmission** | 52 | 71.18 | 0 | 0.00 |
| **Auto-inoculation (non-ocular)** | 62 | 84.86 | 20 | 494.78 |
| **Ocular vaccinia** | 16 | 21.90 | 3 | 74.22 |

[a] 71% primary vaccination; 89% male; median age 28.5 yr
[b] 36% primary vaccination; 36% male; median age 47.1 yr

#### 5.1.3 Myocarditis and Pericarditis in the ACAM2000 Clinical Trial Experience

In clinical trials involving 2983 subjects who received ACAM2000 and 868 subjects who received Dryvax®, ten (10) cases of suspected myocarditis [0.2% (7 of 2983) ACAM2000 subjects and 0.3% (3 of 868) Dryvax® subjects] were identified. The mean time to onset of suspected myocarditis and/or pericarditis from vaccination was 11 days, with a range of 9 to 20 days. All subjects who experienced these cardiac events were naïve to vaccinia. Of the 10 subjects, 2 were hospitalized. None of the remaining 8 cases required hospitalization or treatment with medication. Of the 10 cases, 8 were sub-clinical and were detected only by ECG abnormalities with or without associated elevations of cardiac troponin I. All cases resolved by 9 months, with the exception of one female subject in the Dryvax® group, who had persistent borderline abnormal left ventricular ejection fraction on echocardiogram. The best estimate of risk for myocarditis and pericarditis is derived from the Phase 3 ACAM2000 clinical trials where there was active monitoring for potential of myocarditis and pericarditis. Among vaccinees naïve to vaccinia, 8 cases of suspected myocarditis and pericarditis were identified across both treatment groups, for a total incidence rate of 6.9 per 1000 vaccinees (8 of 1,162). The rate for the ACAM2000 treatment group were similar: 5.7 (95% CI: 1.9-13.3) per 1000 vaccinees (5 of 873 vaccinees) and for the Dryvax® group 10.4 (95% CI: 2.1-30.0) per 1000 vaccinees (3 of 289 vaccinees). No cases of myocarditis and/or pericarditis were identified in 1819 previously vaccinated subjects. The long-term outcome of myocarditis and pericarditis following ACAM2000 vaccination is currently unknown.

### 5.2 Cardiac Disease

Ischemic cardiac events, including fatalities, have been reported following smallpox vaccination; the relationship of these events, if any, to vaccination has not been established. In addition, cases of non-ischemic, dilated cardiomyopathy have been reported following smallpox vaccination; the relationship of these cases to smallpox vaccination is unknown.

There may be increased risks of adverse events with ACAM2000 in persons with known cardiac disease, including those diagnosed with previous

myocardial infarction, angina, congestive heart failure, cardiomyopathy, chest pain or shortness of breath with activity, stroke or transient ischemic attack, or other heart conditions. In addition, subjects who have been diagnosed with 3 or more of the following risk factors for ischemic coronary disease: 1) high blood pressure; 2) elevated blood cholesterol; 3) diabetes mellitus or high blood sugar; 4) first degree relative (for example mother, father, brother, or sister) who had a heart condition before the age of 50; or 5) smoke cigarettes may have increased risks.

### 5.3 Ocular Complications and Blindness

Accidental infection of the eye (ocular vaccinia) may result in ocular complications including keratitis, corneal scarring and blindness. Patients who are using corticosteroid eye drops may be at increased risk of ocular complications with ACAM2000.

### 5.4 Presence of Congenital or Acquired Immune Deficiency Disorders

Severe localized or systemic infection with vaccinia (progressive vaccinia) may occur in persons with weakened immune systems, including patients with leukemia, lymphoma, organ transplantation, generalized malignancy, HIV/AIDS, cellular or humoral immune deficiency, radiation therapy, or treatment with antimetabolites, alkylating agents, high-dose corticosteroids (>10 mg prednisone/day or equivalent for ≥2 weeks), or other immunomodulatory drugs. The vaccine is contraindicated in individuals with severe immunodeficiency [See Contraindications (4)]. Vaccinees with close contacts who have these conditions may be at increased risk because live vaccinia virus can be shed and be transmitted to close contacts.

### 5.5 History or Presence of Eczema and Other Skin Conditions

Persons with eczema of any description such as, atopic dermatitis, neurodermatitis, and other eczematous conditions, regardless of severity of the condition, or persons who have a history of these conditions at any time in the past, are at higher risk of developing eczema vaccinatum. Vaccinees with close contacts who have eczematous conditions, may be at increased risk because live vaccinia virus can shed and be transmitted to these close contacts. Vaccinees with other active acute, chronic or exfoliative skin disorders (including burns, impetigo, varicella zoster, acne vulgaris with open lesions, Darier's disease, psoriasis, seborrheic dermatitis, erythroderma, pustular dermatitis, etc.), or vaccinees with household contacts having such skin disorders might also be at higher risk for eczema vaccinatum.

### 5.6 Infants (< 12 months of Age) and Children

ACAM2000 has not been studied in infants or children. The risk of serious adverse events following vaccination with live vaccinia virus is higher in infants. Vaccinated persons who have close contact with infants, e.g., breastfeeding, must take precautions to avoid inadvertent transmission of ACAM2000 live vaccinia virus to infants.

### 5.7 Pregnancy

ACAM2000 has not been studied in pregnant women. Live vaccinia virus vaccines can cause fetal vaccinia and fetal death. If ACAM2000 is administered during pregnancy, the vaccinee should be apprised of the potential hazard to the fetus [See Use in Specific Populations (8.1)]. Pregnant women who are close contacts of vaccinees may be at increased risk because live vaccinia virus can shed and be transmitted to close contacts.

### 5.8 Allergy to ACAM2000 Smallpox Vaccine or its Components

ACAM2000 contains neomycin and polymyxin B. Persons allergic to these components may be at higher risk for adverse events after vaccination.

Both the vaccine and diluent vial stoppers do not contain latex material.

### 5.9 Management of Smallpox Vaccine Complications

The CDC can assist physicians in the diagnosis and management of patients with suspected complications of vaccinia (smallpox) vaccination. Vaccinia Immune Globulin (VIG) is indicated for certain complications of vaccination live vaccinia virus smallpox vaccine. If VIG is needed or additional information is required, physicians should contact the CDC at (404) 639-3670, Monday through Friday 8 AM to 4:30 PM Eastern Standard Time; at other times call (404) 639-2888.

### 5.10 Prevention of Transmission of Live Vaccinia Virus

The most important measure to prevent inadvertent auto-inoculation and contact transmission from vaccinia vaccination is thorough hand washing after changing the bandage or after any other contact with the vaccination site.

Individuals susceptible to adverse effects of vaccinia virus, i.e., those with cardiac disease, eye disease, immunodeficiency states, including HIV infection, eczema, pregnant women and infants, should be identified and measures should be taken to avoid contact between those individuals and persons with active vaccination lesions.

Recently vaccinated healthcare workers should avoid contact with patients, particularly those with immunodeficiencies, until the scab has separated from the skin at the vaccination site. However, if continued contact with patients is unavoidable, vaccinated healthcare workers should ensure the vaccination site is well covered and follow good hand-washing technique. In this setting, a more occlusive dressing may be used. Semipermeable polyurethane dressings are effective barriers to shedding of vaccinia. However, exudate may accumulate beneath the dressing, and care must be taken to prevent viral spread when the dressing is changed. In addition, accumulation of fluid beneath the dressing may increase skin maceration at the vaccination site. Accumulation of exudate may be decreased by first covering the vaccination with dry gauze, then applying the dressing over the gauze. The dressing should be changed every 1-3 days [See Self Inoculation and Spread to Close Contacts (17.3) and Care of the Vaccination Site and Potentially Contaminated Materials (17.4)].

### 5.11 Blood and Organ Donation

Blood and organ donation should be avoided for at least 30 days following vaccination with ACAM2000.

### 5.12 Limitations of Vaccine Effectiveness

ACAM2000 smallpox vaccine may not protect all persons exposed to smallpox.

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia (vaccinia necrosum), generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including Stevens-Johnson syndrome) and eczema vaccinatum. Severe disability, permanent neurological sequelae, and/or death may occur. Death of unvaccinated individuals who have contact with vaccinated individuals. [See Warnings and Precautions (5.1)].
- Myocarditis and/or pericarditis, ischemic heart disease and non-ischemic, dilated cardiomyopathy [See Warnings and Precautions (5.1)].
- Ocular complications and blindness [See Warnings and Precautions (5.3)].

### 6.1 Overall Adverse Reaction Profile

Information regarding the safety of ACAM2000 has been derived from three sources: 1) ACAM2000 clinical trial experience (Phase 1, 2 and 3 clinical trials), 2) data compiled during the era of routine smallpox vaccination using other NYCBH vaccinia vaccines and 3) adverse event data obtained during military and civilian smallpox vaccination programs (2002-2005) that used Dryvax®, a licensed live vaccinia virus smallpox vaccine.

- General Disorders and Administrative Site Conditions: In the ACAM2000 clinical studies 97% and 92% of vaccinia-naïve and previously vaccinated subjects, respectively, experienced one or more adverse event. Common events included injection site reactions (erythema, pruritus, pain and swelling) and constitutional symptoms (fatigue, malaise, feeling hot, rigors and exercise tolerance decreased). Across all ACAM2000 studies 10% of vaccinia-naïve and 3% of previously vaccinated subjects experienced at least one severe adverse event (defined as interfering with normal daily activities).
- Nervous System Disorder: Overall, 50% and 34% of vaccinia-naïve subjects and previously vaccinated subjects, respectively, reported headaches in ACAM2000 studies. There have been reports of headache following smallpox vaccination which required hospitalization. Although <1% of the subjects in the ACAM2000 program experienced severe headaches, none required hospitalization.

  Neurological adverse events assessed among the 2002 - 2005 military (n=590,400) and DHHS (n=64,600) programs temporally associated with smallpox vaccination included headache (95 cases), non-serious limb paresthesias (17 cases) or pain (13 cases) and dizziness or vertigo (13 cases). Serious neurologic adverse events included 13 cases of suspected meningitis, 3 cases of suspected encephalitis or myelitis, 11 cases of Bell palsy, 9 seizures (including 1 death), and 3 cases of Guillain-Barre syndrome. Among these 39 events, 27 (69%) occurred in primary vaccinees and all but 2 occurred within 12 days of vaccination. There have also been cases of photophobia following smallpox vaccination, some of which required hospitalization.
- Musculoskeletal and Connective Tissue Disorders: Across all ACAM2000 studies, severe, vaccine-related myalgia was seen in 1% of

vaccinia-naïve subjects and <1% of previously vaccinated subjects. Other adverse events included back pain, arthralgia and pain in extremity and none occurred with a frequency of more than 2% in either the vaccinia-naïve or previously vaccinated populations.

- Blood and Lymphatic System Disorders: The only adverse event occurring at ≥5% in the ACAM2000 studies were lymph node pain and lymphadenopathy. The incidence of severe lymph node pain and lymphadenopathy was <1%.
- Gastrointestinal (GI) Disorders: Commonly reported GI disorders among ACAM2000-treated subjects included nausea and diarrhea (14%), constipation (6%), and vomiting (4%). Severe abdominal pain, nausea, vomiting, constipation diarrhea and toothache accounted for all the severe adverse events reported and occurred in <1% of subjects.
- Skin and Subcutaneous Tissue Disorders: Erythema and rash were noted in 18% and 8% of subjects respectively. In ACAM2000 subjects 1% of vaccinia-naïve and <1% of previously vaccinated subjects experienced at least one severe adverse event. With the exception of one case of contact dermatitis and one case of urticaria, erythema and rash accounted for all severe events.

  Generalized rashes (erythematous, papulovesicular, urticarial, folliculitis, nonspecific) are not uncommon following smallpox vaccination and are presumed to be hypersensitivity reactions occurring among persons without underlying illnesses. These rashes are generally self-limited and require little or no therapy, except among patients whose conditions appear to be toxic or who have serious underlying illnesses.

  Inadvertent inoculation at other body sites is the most frequent complication of vaccinia vaccination, usually resulting from autoinoculation of the vaccine virus transferred from the site of vaccination. The most common sites involved are the face, nose, mouth, lips, genitalia and anus. Accidental infection of the eye (ocular vaccinia) may result in ocular complications including, but not limited to, keratitis, corneal scarring and blindness.

  Major cutaneous reactions at the site of inoculation, characterized by large area of erythema and induration and streaking inflammation of draining lymphatics may resemble cellulitis. Benign and malignant lesions have been reported to occur at the smallpox vaccination site.

### 6.2 ACAM2000 Clinical Trial Experience

Two randomized, controlled, multi-center Phase 3 trials enrolled 2244 subjects that received ACAM2000 and 737 that received a comparison licensed live vaccinia virus vaccine, Dryvax®. Study 1 was conducted in male (66% and 63% for ACAM2000 and Dryvax®, respectively) and female (34% and 37% for ACAM2000 and Dryvax®, respectively) subjects who previously had not been vaccinated with smallpox vaccine (i.e., vaccinia-naïve subjects). The majority of subjects were Caucasian (76% and 71% for ACAM2000 and Dryvax®, respectively) and the mean age was 23 in both groups with an age range from 18-30 years. Study 2 was conducted in male (50% and 48% for ACAM2000 and Dryvax®, respectively) and female (50% and 52% for ACAM2000 and Dryvax®, respectively) subjects who had been vaccinated with smallpox vaccine >10 years previously (i.e., previously vaccinated subjects). The majority of subjects were Caucasian (78% for both groups) and the mean age was 49 years in both groups with an age range of 31 to 84 years.

#### 6.2.1 Common Adverse Events Reported in ACAM2000 Clinical Program

Adverse events reported by ≥5% of subjects in either the ACAM2000 or the comparison treatment group during Phase 3 studies are presented by type of adverse events, by baseline vaccination status (vaccinia-naïve versus previously vaccinated) and by treatment group. Severe vaccine-related adverse events, defined as interfering with normal daily activities, in vaccinia-naïve subjects were reported by 10% of subjects in the ACAM2000 group and 13% in the comparison group. In the previously vaccinated subjects, the incidence of severe vaccine-related adverse events was 4% for the ACAM2000 groups and 6% for the comparison group.

**Table 3 - Adverse Events Reported by ≥5% of Subjects in ACAM2000 or Dryvax®**

| | **Study 1 Vaccinia-Naïve Subjects** | | **Study 2 Previously Vaccinated Subjects** | |
|---|---|---|---|---|
| | **ACAM2000 N=873 n (%)** | **Dryvax® N=289 n (%)** | **ACAM2000 N=1371 n (%)** | **Dryvax® N=448 n (%)** |
| **At least 1 adverse event** | **864 (99)** | **288 (100)** | **1325 (97)** | **443 (99)** |
| **Blood and lymphatic system disorders** | **515 (59)** | **204 (71)** | **302 (22)** | **133 (30)** |
| **Lymph node pain[(a)]*** | 494 (57) | 199 (69) | 261 (19) | 119 (27) |
| **Lymphadenopathy** | 72 (8) | 35 (12) | 78 (6) | 29 (6) |
| **Gastrointestinal disorders** | **273 (31)** | **91 (31)** | **314 (23)** | **137 (31)** |
| **Nausea[(a)]** | 170 (19) | 65 (22) | 142 (10) | 63 (14) |
| **Diarrhea[(a)]** | 144 (16) | 34 (12) | 158 (12) | 77 (17) |
| **Constipation[(a)]** | 49 (6) | 9 (3) | 88 (6) | 31 (7) |
| **Vomiting[(a)]** | 42 (5) | 10 (3) | 40 (3) | 18 (4) |
| **General disorders and administration site conditions** | **850 (97)** | **288 (100)** | **1280 (93)** | **434 (97)** |
| **Injection site pruritus[(a)]** | 804 (92) | 277 (96) | 1130 (82) | 416 (93) |
| **Injection site erythema[(a)]** | 649 (74) | 229 (79) | 841 (61) | 324 (72) |
| **Injection site pain[(a)]** | 582 (67) | 208 (72) | 505 (37) | 209 (47) |
| **Fatigue[(a)]** | 423 (48) | 161 (56) | 468 (34) | 184 (41) |
| **Injection site swelling** | 422 (48) | 165 (57) | 384 (28) | 188 (42) |
| **Malaise[(a)]** | 327 (37) | 122 (42) | 381 (28) | 147 (33) |
| **Feeling hot[(a)]** | 276 (32) | 97 (34) | 271 (20) | 114 (25) |
| **Rigors[(a)]** | 185 (21) | 66 (23) | 171 (12) | 76 (17) |
| **Exercise tolerance decreased[(a)]** | 98 (11) | 35 (12) | 105 (8) | 50 (11) |
| **Musculoskeletal and connective tissue disorders** | **418 (48)** | **153 (53)** | **418 (30)** | **160 (36)** |
| **Myalgia[(a)]** | 404 (46) | 147 (51) | 374 (27) | 148 (33) |
| **Nervous system disorders** | 444 (51) | 151 (52) | 453 (33) | 174 (39) |
| **Headache[(a)]** | 433 (50) | 150 (52) | 437 (32) | 166 (37) |
| **Respiratory, thoracic, and mediastinal disorders** | **134 (15)** | **40 (14)** | **127 (9)** | **42 (9)** |
| **Dyspnea[(a)]** | 39 (4) | 16 (6) | 41 (3) | 18 (4) |
| **Skin and subcutaneous tissue disorders** | **288 (33)** | **103 (36)** | **425 (31)** | **139 (31)** |
| **Erythema[(a)]** | 190 (22) | 69 (24) | 329 (24) | 107 (24) |
| **Rash[(a)]** | 94 (11) | 30 (10) | 80 (6) | 29 (6) |

[a] Event was listed on a checklist included in subject diaries; therefore should be considered solicited. In addition to events listed above the following were also included as part of the checklist: chest pain and heart palpitations, but these events did not occur in ≥5% of subjects.

## 7 DRUG INTERACTIONS

### 7.1 Simultaneous Administration with Other Vaccines

There are no data evaluating the simultaneous administration of ACAM2000 with other vaccines.

### 7.2 Interference with Laboratory Tests

ACAM2000 may induce false-positive tests for syphilis. Positive RPR tests results should be confirmed using a more specific test, such as the FTA assay.

ACAM2000 may induce temporary false-negative results for the tuberculin skin test (purified protein derivative [PPD]) and possibly, blood tests for tuberculosis. Tuberculin testing should be delayed if possible for 1 month following smallpox vaccination.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category D

ACAM2000 has not been studied in pregnant women. Live vaccinia virus vaccines can cause fetal harm when administered to a pregnant woman. Congenital infection, principally occurring during the first trimester, has been observed after vaccination with live vaccinia smallpox vaccines, although the risk may be low. Generalized vaccinia of the fetus, early delivery of a stillborn infant, or a high risk of perinatal death has been reported.

The only setting in which vaccination of pregnant women should be considered is when exposure to smallpox is considered likely. If this vaccine is used during pregnancy, or if the vaccinee lives in the same household with or has close contact with a pregnant woman, the vaccinee should be apprised of the potential hazard to the fetus. Healthcare providers, state health departments, and other public health staff should report to the National Smallpox Vaccine in Pregnancy Registry all pregnant women who, from 42 days prior to conception onward, received ACAM2000 or had close contact with a person who received ACAM2000 within the previous 28 days.. Civilian women should contact their healthcare provider or state health department for help enrolling in the registry. All civilian and military cases should be reported to the DoD, telephone 619 553-9255, Defense Switched Network (DSN) 553-9255, fax 619 533-7601 or e-mail NHRC-BirthRegistry@med.navy.mil**.**

### 8.3 Nursing Mothers

ACAM2000 has not been studied in lactating women. It is not known whether vaccine virus or antibodies are secreted in human milk. Live vaccinia virus can be inadvertently transmitted from a lactating mother to her infant. Infants are at high risk of developing serious complications from live vaccinia smallpox vaccination.

### 8.4 Pediatric Use

The safety and effectiveness of ACAM2000 have not been established in the age groups from birth to age 16. The use of ACAM2000 in all pediatric age groups is supported by evidence from the adequate and well-controlled studies of ACAM2000 in adults and with additional historical data with use of live vaccinia virus smallpox vaccine in pediatrics. Before the eradication of smallpox disease, live vaccinia virus smallpox vaccine was administered routinely in all pediatric age groups, including neonates and infants, and was effective in preventing smallpox disease. During that time, live vaccinia virus was occasionally associated with serious complications in children, the highest risk being in infants younger than 12 months of age. [See Warnings and Precautions (5.6)].

### 8.5 Geriatric Use

Clinical studies of ACAM2000 did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. There are no published data to support the use of this vaccine in geriatric (persons >65 years) populations.

## 11 DESCRIPTION

ACAM2000, Smallpox (Vaccinia) Vaccine, Live, is a live vaccinia virus derived from plaque purification cloning from Dryvax® (Wyeth Laboratories, Marietta, PA, calf lymph vaccine, New York City Board of Health Strain) and grown in African Green Monkey kidney (Vero) cells and tested to be free of adventitious agents.

ACAM2000 is provided as a lyophilized preparation of purified live virus containing the following non-active excipients: 6-8 mM HEPES (pH 6.5-7.5), 2% human serum albumin USP, 0.5 – 0.7% sodium chloride USP, 5% mannitol USP, and trace amounts of neomycin and polymyxin B.

Diluent for ACAM2000 contains 50% (v/v) Glycerin USP, 0.25% (v/v) Phenol USP in Water for Injection USP, supplied in 3 mL clear glass vials containing 0.6 mL of diluent.

After reconstitution, each vial of ACAM2000 vaccine contains approximately 100 doses (0.0025 mL/dose). The concentration of vaccinia virus is 1.0-5.0 x $10^8$ plaque-forming units (PFU)/mL or 2.5-12.5 x $10^5$ PFU/dose determined by plaque assay in Vero cells. ACAM2000 is administered by the percutaneous route (scarification) using 15 jabs of a stainless steel bifurcated needle that has been dipped into the vaccine.

## 12 CLINICAL PHARMACOLOGY

Smallpox vaccine does not contain smallpox virus (variola) and cannot spread or cause smallpox.

### 12.1 Mechanism of Action

Vaccinia virus is a member of the same taxonomic group (the Orthopox genus) as smallpox (variola) virus, and immunity induced by vaccinia virus cross-protects against variola virus. Vaccinia virus causes a localized virus infection of the epidermis at the site of inoculation, surrounding dermal and subcutaneous tissues, and draining lymph nodes. Virus may be transiently present in blood and infects reticuloendothelial and other tissues. Langerhans cells in the epidermis are specific targets for the early stage of virus replication. The formation of a pustule ('pock' or 'take') at the site of inoculation provides evidence of protective immunity. The virus replicates within cells and viral antigens are presented to the immune system. Neutralizing antibodies and B and T cells provide long-term memory. The level of neutralizing antibody that protects against smallpox is unknown but >95% of persons undergoing primary vaccination develop neutralizing or hemagglutination inhibiting antibodies to vaccinia.

### 12.2 Pharmacodynamics

#### 12.2.1 Cutaneous Response

The cutaneous responses following smallpox vaccination are dependent on the immune status of the individual, potency of the vaccine, and vaccination technique. Two types of responses have been defined by the WHO Expert Committee on Smallpox, and described by the Advisory Committee on Immunization Practices (ACIP). The responses include: a) major cutaneous reaction, which indicates that virus replication has taken place and vaccination was successful; or b) equivocal reaction. Equivocal reactions may be a consequence of pre-existing immunity adequate to suppress viral multiplication, vaccination technique failure, or use of inactive vaccine or vaccine that has lost potency.

Successful vaccination in persons who are naïve to smallpox vaccination, termed primary vaccination, is represented by a major cutaneous reaction, defined as a vesicular or pustular lesion or an area of definite palpable induration or congestion surrounding a central lesion that might be a crust or an ulcer.

Subjects who have been previously vaccinated and are revaccinated may manifest a reduced cutaneous response compared to vaccinia-naïve subjects, but still exhibit an immune response to the vaccine. [See Dosage and Administration (2.4)]

#### 12.2.2 Neutralizing Antibody and Cellular Immune Responses

Neutralizing antibodies are known to mediate protection against smallpox. Neutralizing antibodies against vaccinia develop in >95% of individuals following primary vaccination, rise rapidly (by day 15-20 after vaccination) and may be boosted on revaccination. Antibody titers are highly variable. Titers may remain high for longer periods following two or more vaccinations than after a primary vaccination. The level of the neutralizing antibody response following primary vaccination is generally in proportion to the intensity of the cutaneous reaction. The level of neutralizing antibody that is required to protect against smallpox has not been clearly established, although some studies indicate that persons with antibody titers > 1:32 are protected. Cellular immune responses are also elicited by vaccination and may contribute to protection and immunological memory.

#### 12.2.3 Virus Shedding

Virus is shed from the vaccination site during the period starting with the development of a papule (day 2-5); shedding ceases when the scab separates and the lesion is re-epithelialized, about 14-21 days after vaccination. Steps should be taken in clinical use to reduce the risk of accidental infection of other sites in the vaccinated patient or of contact spread to other individuals [See Vaccination Instructions (2.3)].

## 14 CLINICAL STUDIES

Vaccine efficacy was assessed by comparing the immunologic response of ACAM2000 to another US-licensed live vaccinia virus smallpox vaccine, Dryvax®, in two randomized, multi-center active-controlled clinical trials; one study in subjects who previously had not been vaccinated with smallpox vaccine (i.e., vaccinia-naïve subjects) and one study in subjects who had been vaccinated with smallpox vaccine >10 years previously (i.e., previously vaccinated subjects). In both trials, the co-primary efficacy endpoints were the proportion of subjects with a successful vaccination/revaccination and the geometric mean neutralizing antibody titer (GMT) on Day 30. Successful primary vaccination was defined as a major cutaneous reaction on Day 7 or 10 (Days 6 to 11, with allowable visit window). Successful revaccination was defined as development of any cutaneous lesion on Day 7 (± 1 day) of a measurable size. Successful revaccination was determined by a panel of experts who reviewed digital photographs of the cutaneous lesions.

The statistical method used to compare the proportion of subjects who were successfully vaccinated in the two treatment groups was a test of non-inferiority of ACAM2000 to the active comparator intended to rule out a greater than 5% margin of superiority of the comparator for successful primary vaccination (Study 1) and a 10% margin of superiority of the comparator for successful revaccination (Study 2). Non-inferiority was to be declared if the lower bound of the 1-sided 97.5% confidence interval (CI) for the percent difference between ACAM2000 and the comparator exceeded -5% in naïve subjects and -10% in previously vaccinated subjects.

Analysis of the GMT was performed using a test of non-inferiority of neutralizing antibody titer between ACAM2000 and the comparator, intended to ensure that the ratio of the GMTs of ACAM2000: comparator vaccine was at least 0.5 (equivalent to the difference of the $\log_{10}$ (GMT) being at least -0.301).

In Study 1, a total of 1037 male and female vaccinia-naïve subjects, aged 18 to 30 years inclusive, primarily Caucasian (76%) were randomized in a 3:1 ratio to receive ACAM2000 (780 subjects) or comparator (257 subjects). The ACAM2000 subjects were further stratified to receive one of three lots (Lots A, B and C) at a 1:1:1 ratio (258, 264, and 258 subjects, respectively). All subjects were to be evaluated for their cutaneous response and a random subset was selected for evaluation of neutralizing antibody response.

In Study 2, a total of 1647 male and female previously-vaccinated subjects, aged 31 to 84 years inclusive, primarily Caucasian (81%) were randomized in a 3:1 ratio to receive ACAM2000 (1242 subjects) or the comparator (405 subjects). The ACAM2000 subjects were further stratified to receive one of three lots (Lots A, B and C) at a 1:1:1 ratio (411, 417, and 414 subjects, respectively). All subjects were evaluated for their cutaneous response and a random subset was to be selected for evaluation of neutralizing antibody response.

Table 4 presents the results of the primary efficacy analyses for both studies.

**Table 4 - – Cutaneous Response (Vaccination Success) and Neutralizing Antibody Response in Subjects Given ACAM2000 Vs. Comparator Vaccine**

| | **Study Population / Treatment Group** | | | |
|---|---|---|---|---|
| | **Study 1 Vaccinia-Naïve Subjects** | | **Study 2 Previously Vaccinated Subjects** | |
| | **ACAM 2000** | **Comparator** | **ACAM 2000** | **Comparator** |
| **Cutaneous Response (Vaccination Success)** | | | | |
| Size of Evaluable Population[a] | 776 | 257 | 1189 | 388 |
| Number of Vaccination Successes (%) | 747 (96)[b] | 255 (99) | 998 (84)[h] | 381 (98) |
| 97.5% 1-sided CI by normal approx. on percent difference between ACAM2000-Comparator | -4.67% [c] | | -17% [i] | |
| Non-Inferiority to Comparator | Yes | | No | |
| **Neutralizing Antibody Response ( based on $PRNT_{50}$[d] Titer on Day 30)** | | | | |
| Size of Evaluable Population[e] | 565 | 190 | 734 | 376 |
| GMT[f] | 166 | 255 | 286 | 445 |
| $Log_{10}$ mean | 2.2 | 2.4 | 2.5 | 2.6 |
| 97.5% 1-sided CI by ANOVA on difference between ACAM2000-Comparator | -0.307[g] | | -0.275[j] | |
| Meets Non-Inferiority to Comparator | No | | Yes | |

a Subjects who received study vaccine and were evaluated for a local cutaneous reaction within the protocol-designated timeframe were included in the efficacy evaluable (EE) population.

b Results for vaccine lots, A, B and C were 95%, 98% and 96%.

c Since the critical value for the evaluation was declared to be -5%, ACAM2000 is considered to be non-inferior to Comparator for this parameter.

d $PRNT_{50}$ – Vaccinia 50% plaque reduction neutralization test.

e A randomly selected sample of subjects who received study vaccine and had samples collected for neutralizing antibody response at Baseline and at the designated time-point post-treatment were included in the antibody evaluable (AnE) population.

f GMT – Geometric mean neutralizing antibody titer.

g Since the critical value for the evaluation was declared to be -0.301, ACAM2000 is not considered to be non-inferior to Comparator for this parameter.

h Results for vaccine lots, A, B and C were 79%, 87% and 86%.

i Since the critical value for the evaluation was declared to be -10%, ACAM2000 is not considered to be non-inferior to Comparator for this parameter.

j Since the critical value for the evaluation was declared to be -0.301, ACAM2000 is considered to be non-inferior to Comparator for this parameter.

The primary determinant for an effective immune response in those naïve to vaccine is a major cutaneous reaction. ACAM2000 was non-inferior to comparator in this population with regard to eliciting a major cutaneous reaction. The measure of the strength of the generated antibody response was similar but did not meet the predefined criterion for non-inferiority. Among subjects who were previously vaccinated, development of a major cutaneous response after revaccination with vaccinia-based smallpox vaccines may not provide an accurate measure of the strength of the immune response because the pre-existing immunity modifies the scope of the cutaneous response. In previously vaccinated subjects, ACAM2000 was non-inferior to the comparator with regard to the strength of the neutralizing antibody immune response. Therefore, ACAM2000 was non-inferior to the comparator in the rate of major cutaneous reaction in those naïve to the vaccine, and the strength of the neutralizing antibody immune response in those previously exposed to vaccinia-based smallpox vaccines.

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## 16 HOW SUPPLIED / STORAGE AND HANDLING

### 16.1 How Supplied

ACAM2000, Smallpox (Vaccinia) Vaccine, Live, is supplied in multiple-dose 3 mL clear glass vials containing lyophilized powder (freeze-dried vaccine). After reconstitution with 0.3 mL of diluent, the vial contains approximately 100 nominal doses of 0.0025 mL of vaccinia virus (live), 1.0 - $5.0 \times 10^8$ PFU/mL or 2.5-$12.5 \times 10^5$ PFU/dose.

Diluent for ACAM2000, 50% (v/v) Glycerin USP, 0.25% (v/v) Phenol USP in Water for Injection USP, is supplied in 3 mL clear glass vials containing 0.6 mL of diluent.

Bifurcated needles are supplied in boxes (5 x 5 x 1 in) containing 100 needles.

1 mL tuberculin syringes with 25 gauge x 5/8" needles are supplied for vaccine reconstitution.

### 16.2 Storage and Handling

ACAM2000 should be stored in a freezer with an average temperature of -15°C to -25°C (+5°F to -13°F).

Prior to reconstitution, ACAM2000 vaccine retains a potency of $1.0 \times 10^8$ PFU or higher per dose for at least 18 months when stored at refrigerated temperatures of +2-8°C (36-46°F).

During shipment, ACAM2000 should be maintained at a temperature of

-10°C or colder.

After reconstitution, ACAM2000 vaccine may be administered during a 6 to 8 hour workday at room temperature (20-25°C, 68-77°F). Reconstituted ACAM2000 vaccine may be stored in a refrigerator (2-8°C, 36-46°F) no longer than 30 days, after which it should be discarded [*See Dosage and Administration (2.3)*]. Diluent for Smallpox Vaccine, (Vero Cells) Lyophilized, ACAM2000 should be stored at room temperature (15-30°C, 59-86°F). ACAM2000 contains live vaccinia virus that is transmissible, and should be handled as an infectious agent once vials are open. See 2.1 [Instructions for Vaccine Preparation] and 2.2 [Preparation / Handling Precautions and Instructions for Disposal] for details on handling and disposal.

## 17 PATIENT COUNSELING INFORMATION

Please refer patient to the FDA-approved Medication Guide prepared for ACAM2000 Smallpox Vaccine.

### 17.1 Serious Complications of Vaccination

Patients must be informed of the major serious adverse events associated with vaccination, including myocarditis and/or pericarditis, progressive vaccinia in immunocompromised persons, eczema vaccinatum in persons with skin disorders, auto- and accidental inoculation, generalized vaccinia, urticaria, erythema multiforme major (including Stevens-Johnson syndrome) and fetal vaccinia in pregnant women.

### 17.2 Protecting Contacts at Highest Risk for Adverse Events

Patients must be informed that they should avoid contact with individuals at high risk of serious adverse effects of vaccinia virus, for instance, those with past or present eczema, immunodeficiency states including HIV infection, pregnancy, or infants less than 12 months of age.

### 17.3 Self-inoculation and Spread to Close Contacts

Patients must be advised that virus is shed from the cutaneous lesion at the site of inoculation from approximately Day 3 until scabbing occurs, typically between Days 14-21 after primary vaccination. Vaccinia virus may be transmitted by direct physical contact. Accidental infection of skin at sites other than the site of intentional vaccination (self-inoculation) may occur by trauma or scratching. Contact spread may also result in accidental inoculation of household members or other close contacts. The result of accidental infection is a pock lesion(s) at an unwanted site(s) in the vaccinee or contact, and resembles the vaccination site. Self-inoculation occurs most often on the face, eyelid, nose, and mouth, but lesions at any site of traumatic inoculation can occur. Self-inoculation of the eye may result in ocular vaccinia, a potentially serious complication.

### 17.4 Care of the Vaccination Site and Potentially Contaminated Materials

Patients must be given the following instructions:

- The vaccination site must be completely covered with a semipermeable bandage. Keep site covered until the scab falls off on its own.
- The vaccination site must be kept dry. Normal bathing may continue, but cover the vaccination site with waterproof bandage when bathing. The site should not be scrubbed. Cover the vaccination site with loose gauze bandage after bathing.
- Don’t scratch the vaccination site. Don’t scratch or pick at the scab.
- Do not touch the lesion or soiled bandage and subsequently touch other parts of the body particularly the eyes, anal and genital areas that are susceptible to accidental (auto-) inoculation.
- After changing the bandage or touching the site, wash hands thoroughly with soap and water or >60% alcohol-based hand-rub solutions.
- To prevent transmission to contacts, physical contact of objects that have come into contact with the lesion (e.g. soiled bandages, clothing, fingers) must be avoided.
- Wash separately clothing, towels, bedding or other items that may have come in direct contact with the vaccination site or drainage from the site, using hot water with detergent and/or bleach. Wash hands afterwards.
- Soiled and contaminated bandages must be placed in plastic bags for disposal.
- The vaccinee must wear a shirt with sleeves that covers the vaccination site as an extra precaution to prevent spread of the vaccinia virus. This is particularly important in situations of close physical contact.
- The vaccinee must change the bandage every 1 to 3 days. This will keep skin at the vaccination site intact and minimize softening.
- Don’t put salves or ointments on the vaccination site.
- When the scab fall off, throw it away in a sealed plastic bag and wash hands afterwards.