

AUSTRALIAN PRODUCT INFORMATION – ACAM2000® SMALLPOX VACCINE (LIVE VACCINIA VIRUS) LYOPHILIZED POWDER AND DILUENT

1 NAME OF THE MEDICINE

ACAM 2000 smallpox vaccine (live vaccinia virus).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ACAM2000 is provided as a lyophilized preparation of purified live virus

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 10⁸ plaque-forming units (PFU)/mL or 2.5-12.5 x 10⁵ PFU/dose determined by plaque assay in Vero cells.

The product contains 2% albumin USP and trace amounts of neomycin sulfate and polymyxin B sulfate.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

ACAM2000 Smallpox Vaccine 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 presented as a lyophilized powder and diluent. ACAM2000 is a white to off white lyophilized powder. The diluent is a clear colourless solution. ACAM2000 is administered by the percutaneous route (scarification) using 15 jabs of a stainless steel bifurcated needle that has been dipped into the vaccine.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ACAM2000 is indicated for active immunization against smallpox disease for persons determined to be at high risk for smallpox infection in an officially declared outbreak.

4.2 DOSE AND METHOD OF ADMINISTRATION

ACAM2000 should be administered only by vaccine providers with training to safely and effectively administer the vaccine by the percutaneous route (scarification). ACAM2000 should not be injected by the intradermal, subcutaneous, intramuscular, or intravenous route.

Instructions for Vaccine Preparation

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 contents 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 Section 4.2 - Dose and Method of Administration; *Preparation / Handling Precautions and Instructions for Disposal.*]

Storage following Reconstitution

After reconstitution, ACAM2000 vaccine may be administered within 6 to 8 hours if kept at room temperature (20-25°C); it should then be discarded as a biohazardous material. Unused, reconstituted ACAM2000 vaccine may be stored in a refrigerator (2-8°C) up to 30 days, after which it should be discarded as a biohazardous material. [See Section 4.2 - Dose and Method of Administration; *Preparation / Handling Precautions and Instructions for Disposal.*] Exposure of reconstituted vaccine to room temperature during vaccination sessions should be minimized by placing it in refrigerator or on ice between patient administrations.

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

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, or any other surface.

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 Section 4.2 - Dose and Method of Administration; *Storage Following Reconstitution.*]

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 (semioclusive) 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.

Instructions for Interpreting Vaccination Response

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.

Previously Vaccinated Individuals (Revaccination)

Successful vaccination in an individual previously exposed to vaccine is confirmed when a major cutaneous reaction [see Section 4.2 - Dose and Method of Administration; *Primary Vaccinees* 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.

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 Section 4.2, Dose and Method of Administration; *Vaccination Instructions*.

If a repeat vaccination is conducted using vaccine from another vial or vaccine lot fails to produce a major reaction, healthcare providers should consult their health department before giving another vaccination.

Figure 1 Progression of major cutaneous reaction after primary vaccination

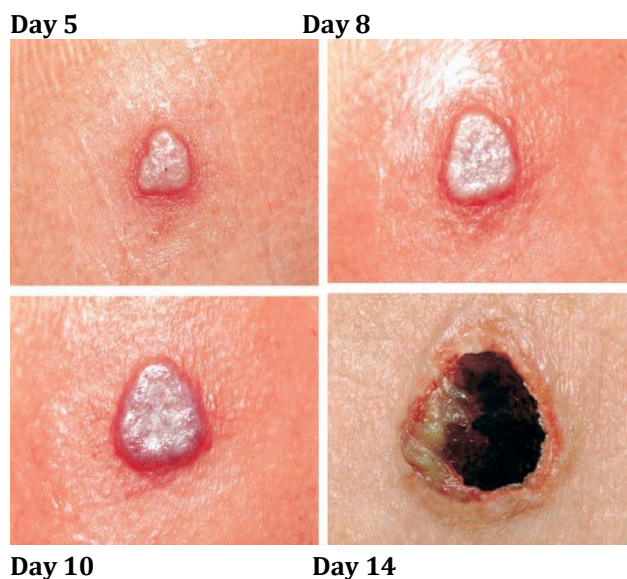
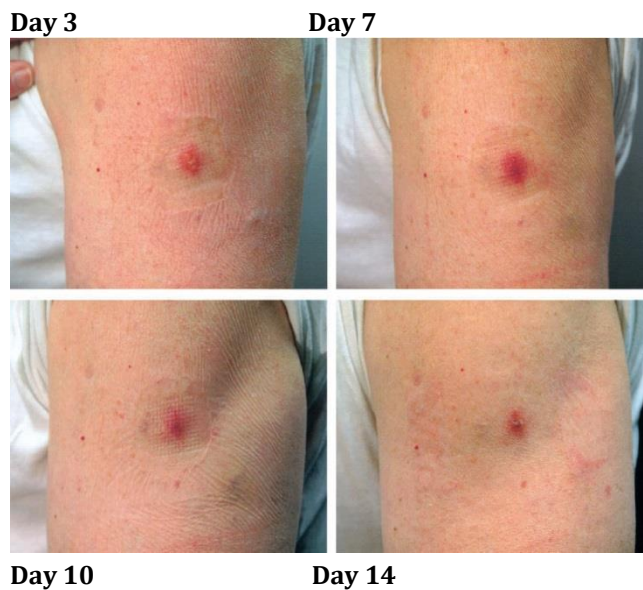


Figure 2 Progression of major cutaneous reaction after revaccination



Booster Schedule

PERSONS AT CONTINUED HIGH RISK OF EXPOSURE TO SMALLPOX AND RELATED LIVE POX VIRUSES (E.G., RESEARCH LABORATORY WORKERS HANDLING ORTHOPOX VIRUSES) SHOULD RECEIVE ACAM2000 VACCINATION EVERY THREE YEARS.

4.3 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 Section 4.4 - Special Warnings and Precautions for Use for persons who are at higher risk of experiencing serious vaccination complications.

The individuals who are at high risk of experiencing serious vaccination complications should not receive ACAM2000 unless they have been exposed to smallpox.

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 states who require isolation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

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 vaccinia 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 sequelae 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 pericarditis 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, postvaccinia encephalitis, progressive vaccinia, or eczema vaccinatum. Death has also been reported in unvaccinated contacts accidentally infected by individuals who have been vaccinated.

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. 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.
- b. See article for descriptions of complications.
- 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 ^(h)
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.

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

Adverse event	N ^(a)	Incidence /million	N ^(b)	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 (nonocular)	62	84.86	20	494.78
Ocular vaccinia	16	21.90	3	74.22

- Department of Defense program (n=730,580) as of Jan05 where 71% primary vaccination; 89% male; median age 28.5 yr.
- Department of Health and Human Services program (n=40,422) as of Jan04 where 36% primary vaccination; 36% male; medium age 47.1 yr.

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.

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.

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.

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, or 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]. 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.

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.

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 stoppers are not made with natural rubber latex.

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.

Blood and Organ Donation

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

Limitations of Vaccine Effectiveness

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

Advice for Patients receiving ACAM2000

The patient must be advised of the following information, which is also contained in the Consumer Medicine Information.

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, and erythema multiforme major (including Stevens-Johnson syndrome) and fetal vaccinia in pregnant women.

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.

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.

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.
- Avoid scratching 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 have come in 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 falls off, throw it away in a sealed plastic bag and wash hands afterwards.

Use in the elderly

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.

Paediatric 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 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 vaccination was administered routinely in all pediatric age groups, including neonates and infants, and was effective in prevention of smallpox disease. During that time, smallpox vaccine was rarely associated with serious complications in children, the highest risk being in infants younger than 12 months of age. [See Section 4.4 - Special Warnings and Precautions for Use; Serious complications and Death.]

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.

Effects on 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No studies have been conducted to assess potential effects of ACAM2000 vaccine on fertility.

Use in 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 because live vaccinia virus can shed and be transmitted to close contacts.

Use in lactation.

ACAM2000 has not been studied in lactating women. It is not known whether vaccinia 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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, 51% and 35% of vaccinia-naïve subjects and previously vaccinated subjects, respectively, reported nervous system disorder in ACAM2000 studies. Headache was the majority of events with 50% in the vaccinia-naïve subjects and 34% in previously vaccinated subjects. 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.

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®

	ACAM2000 N=873^(b) n (%)	Dryvax® N=289^(b) n (%)	ACAM2000 N=1371^(c) n (%)	Dryvax® N=448^(c) 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 $\geq 5\%$ of subjects.
 - b. Study 1 Vaccinia Naïve Subjects
 - c. Study 2 Previously Vaccinated Subjects

Other adverse events that are historically associated with smallpox vaccine are:

- Encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia (vaccinia necrosum), generalized vaccinia, severe vaccinia 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.
- Myocarditis and /or pericarditis, ischemic heart disease and non-ischemic, dilated cardiomyopathy.
- Ocular complications and blindness. (Please refer to Section 4.4 - Special Warnings and Precautions; Ocular complications and Blindness.)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

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.

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 US 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 Section 4.2 - Dose and Method of Administration]

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.

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 Section 4.2 - Dose and Method of Administration; Vaccination Instructions.]

Clinical trials

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.

Tables 4 and 5 present the results of the primary efficacy analyses for both studies.

Table 4 - Cutaneous Response (Vaccination Success) in Subjects Given ACAM2000 Vs. Comparator Vaccine, Studies 1 and 2

	Study Population / Treatment Group			
	Study 1 Vaccinia-Naïve Subjects		Study 2 Previously Vaccinated Subjects	
	Study 1 ACAM 2000	Study 1 Comparator	Study 2 ACAM 2000	Study 2 Comparator
Size of Evaluable Population ^(a)	776	257	1189	388
Number of Vaccination Successes (%)	747 (96) ^(b)	255 (99)	998 (84) ^(d)	381 (98)
97.5% 1-sided CI by normal approx. on percent difference between ACAM2000-Comparator	-4.67% ^(c)		-17% ^(e)	

Non-Inferiority to Comparator	Yes	No
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- 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.
- Results for vaccine lots, A, B and C were 95%, 98% and 96%.
- Since the critical value for the evaluation was declared to be -5%, ACAM2000 is considered to be non-inferior to Comparator for this parameter
- Results for vaccine lots, A, B and C were 79%, 87% and 86%.
- 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

Table 5 - Neutralizing Antibody Response in Subjects Given ACAM2000 Vs. Comparator Vaccine, Studies 1 and 2

	Study 1 ACAM2000	Study 1 Comparator	Study 2 ACAM2000	Study 2 Comparator
Size of Evaluable Population ^(a)	565	190	734	376
GMT ^(b)	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 ^(c)	--	-0.275 ^(d)	--
Meets Non-Inferiority to Comparator	No	--	Yes	--

- 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.
- GMT – Geometric mean neutralizing antibody titer as measured by Vaccinia 50% plaque reduction neutralization test.
- 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
- 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

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.

5.2 PHARMACOKINETIC PROPERTIES

No data available.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No studies have investigated the genotoxic potential of ACAM2000 vaccine.

Carcinogenicity

No studies have investigated the carcinogenic potential of ACAM2000 vaccine.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

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

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

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

ACAM2000 should be stored in a freezer with an average temperature of -15°C to -25°C.

Prior to reconstitution, ACAM2000 vaccine retains a potency of 1.0×10^8 PFU or higher per dose for at least 18 months when stored at refrigerated temperatures of +2-8°C.

Unused, reconstituted ACAM2000 vaccine may be stored in a refrigerator (2-8°C) no longer than 30 days, after which it should be discarded. [See Dosage and Administration]

During shipment, ACAM2000 should be maintained at a temperature of -10°C or colder.

Diluent for Smallpox Vaccine, (Vero Cells) Lyophilized, ACAM2000 should be stored at room temperature (15-30°C).

ACAM2000 contains live vaccinia virus that is transmissible, and should be handled as an infectious agent once vials are open. See Section 4.2 – Dose and Method of Administration; Instructions for Vaccine Preparation and Preparation / Handling Precautions and Instructions for Disposal for details on handling and disposal.

6.5 NATURE AND CONTENTS OF CONTAINER

ACAM2000 is supplied in multiple-dose 3mL glass vials containing lyophilized powder. After reconstitution each vial of ACAM2000 vaccine contains approximately 100 doses (0.0025 mL/dose).

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

The rubber stoppers for the vaccine and diluent do not contain any latex material.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

After reconstitution, ACAM2000 vaccine may be administered during a 6 to 8 hour workday at room temperature (20-25°C). However, for microbiological reasons, the vaccine should be used as soon as possible after reconstitution. At the end of the vaccination session, any contents remaining should be discarded as a biohazardous material. Unused, reconstituted ACAM2000 vaccine may be stored in a refrigerator (2-8°C) no longer than 30 days, after which it should be discarded. [See Section 4.2 - Dosage and Administration].

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

No data available.

CAS number

No data available.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 –Prescription Only Medicine

8 SPONSOR

Emergent Sales and Marketing Australia Pty. Ltd.

Suite 303
74 Pitt Street
Sydney NSW 2000
Australia

9 DATE OF FIRST APPROVAL

26 August 2009

10 DATE OF REVISION

17 June 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformatting according to new Australia PI template
1	Established name for the product was revised to align with U.S. and other international labeling
4.2	Additional text was added to Subsection “Vaccination Instructions” to provide further clarity in response to product complaints (U.S).
4.2	Addition of ‘ALT Text’ to Figures 1 and 2 as an accessibility aid and to allow the information to be more accessible to people with special needs.
4.4	Table 2 was reformatted to align with accessibility standards (Web Content Accessibility Guidelines); content of table is unchanged.
4.4	Subsection “Presence of Congenital or Acquired Immune Deficiency Disorders” has been supplemented for harmonization with current U.S. Prescribing Information.
4.4	Subsection “Advice for Patients Receiving ACAM2000” was revised to provide more explicit instructions (i.e. replace “should” with “must”).
4.8	Table 3 was reformatted to align with accessibility standards (Web Content Accessibility Guidelines); content of table is unchanged
5.1	Table 4 was split into 2 tables: Table 4—cutaneous reactions and Table 5—antibody response. Content of table is unchanged.
8.0	Sponsor details were revised to reflect transfer of sponsorship to Emergent.