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* Revised: Sep. 2023

Virus vaccines
Biological products, powerful drug, prescription-only drug Note)
Japanese Pharmacopoeia, Minimum Requirements for Biological Products
Freeze-dried Smallpox Vaccine Prepared in Cell Culture

Standard Commodity Classification No. of Japan
876313

Freeze-dried Smallpox Vaccine Prepared in Cell Culture LC16 "KMB"

Storage: Store at −20°C or below.
Shelf Life: 10 years from the date of passing the national test for lot-release

Approval No.	15500EZZ00960
Date of Initial Marketing in Japan	January 2004

Note) Caution - Use only pursuant to the prescription of a physician.

2. PERSONS UNSUITABLE FOR VACCINATION (Persons in whom vaccination is inappropriate)

2.1 Persons with obvious fever
2.2 Persons who are known to have a serious acute disease
2.3 Persons with a history of apparent anaphylaxis to ingredients of this drug
2.4 Immunocompromised person or person receiving immunosuppressive treatment [See 10.1.]
2.5 Person who is known to be pregnant [See 9.5.]
2.6 Person who has an epidemic skin disease that may cause complication via smallpox/mpox vaccination
2.7 Persons who are in a condition inappropriate for vaccination in addition to those listed above

3. SUMMARY OF MANUFACTURING METHOD, COMPOSITION, AND PRODUCT DESCRIPTION

3.1 Summary of Manufacturing Method

This product is a freeze-dried product manufactured by growing live vaccinia virus (LC16m8 strain) in primary rabbit kidney cells not infected with infectious diseases, diluting the obtained virus solution, and dispensing the solution with a stabilizer.
This product uses a bovine blood-derived ingredient (serum), bovine milk-derived ingredients (lactalbumin and casein), and swine-derived ingredients (trypsin, peptone, and enzyme) in its manufacturing process.

3.2 Composition

The following ingredients are contained in 0.5 mL of a solution of this product reconstituted with 0.5 mL of the co-packed diluent (water for injection containing 20 vol% glycerin).

* Active ingredient	Live vaccinia virus (LC16m8 strain) Not less than 5.0×10^7PFU Note)
Excipients	D-Sorbitol 5 w/v% Peptone 5 w/v% Phenol red Not more than 0.002 w/v% Gelatin Not more than 0.15 w/v% 199 Medium Remaining amount pH regulator Suitable amount Concentrated glycerin 20 vol%

This vaccine contains not more than 100 μg (potency) of streptomycin sulfate for injection and not more than 12.5 μg (potency) of erythromycin lactobionate used in the manufacturing process of the drug substance.

*Note) PFU:plaque forming unit (Titer measured as plaque forming units)
Approximate potency (infectious unit) of the vaccine per dose is no less than 1.5×10^5 PFU/dose.

3.3 Product Description

Description	This product is a yellowish freeze-dried product. When reconstituted with the copacked diluent, it becomes a yellowish or reddish clear or slightly turbid liquid.

**4. INDICATIONS

Prevention of smallpox and mpox

**5. PRECAUTIONS CONCERNING INDICATIONS

Prior to vaccination to patients with human immunodeficiency virus infection, it should be confirmed that CD4-positive cell count is 200 cells/μL or more. There is no experience of administering this vaccine to patients with human immunodeficiency virus infection whose CD4-positive cell count is less than 200 cells/μL.

6. DOSAGE AND ADMINISTRATION

This product is reconstituted with 0.5 mL of the co-packed diluent (water for injection containing 20 vol% glycerin), and is generally inoculated into the skin by the multiple puncture technique using a bifurcated needle.

7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION

7.1 Subjects of Vaccination

This product is indicated for persons aged 1 year or older.[1)]

7.2 Interval after Administration of Other Live Vaccines (Injections)

This product should be administered at least 27 days after administration of another live vaccine (injection) in principle. [See 10.2.]

7.3 Simultaneous Vaccination

If the physician considers it necessary, the vaccine can be administered simultaneously with other vaccines. [See 14.3.1.].

8. IMPORTANT PRECAUTIONS

8.1 This drug should be used in compliance with the "Enforcement Regulations of Immunization" and "Guidelines for the Implementation of Routine Vaccinations".
8.2 The health status of the recipient should be fully examined before vaccination through history taking, body temperature measurement, and medical examination (e.g., inspection and auscultation).
8.3 This product contains stock solution-derived gelatin (not more than 0.15 w/v%). Cases of shock and anaphylaxis (e.g., urticaria, dyspnoea, lip oedema, laryngeal oedema) have been reported with administration of gelatin-containing products; the recipient should be interviewed carefully before vaccination and monitored carefully after vaccination. [See 9.1.1 and 11.1.1.]
8.4 This product contains streptomycin as an excipient; it may cause hypersensitivity in individuals sensitive to this ingredient. After vaccination, the vaccine recipient should be monitored carefully, and if any symptom is observed, appropriate measures should be taken.
8.5 The vaccine recipient or his/her guardian should be instructed in advance to avoid excessive exercise on the day of vaccination, keep the vaccination site clean, pay attention to health monitoring after vaccination, and seek immediate medical attention in the case of any abnormal local reaction, change in physical condition, or abnormal symptoms such as high fever, convulsion, and serious skin symptoms.

9. PRECAUTIONS CONCERNING PERSONS WITH SPECIFIC BACKGROUNDS

9.1 Persons to Be Vaccinated with Caution (Persons in Whom the Decision to Vaccinate Must Be Made with Caution)

If a recipient meets any of the following criteria, vaccination should be administered with care after carefully performing medical examination and making a judgment on the appropriateness of vaccination in consideration of his/her health status and constitution, giving sufficient explanation about the necessity, adverse reactions, and usefulness of vaccination, and successfully obtaining his/her consent.

9.1.1 Person with a history of hypersensitivity such as shock or anaphylaxis (e.g., urticaria, dyspnoea, lip oedema, laryngeal oedema) to gelatin-containing pharmaceutical preparations or gelatin-containing foods

[See 8.3.]

9.1.2 Persons with underlying diseases such as cardiovascular disease, renal disease, hepatic disease, hematological disease, and developmental disturbance

[See 9.2 and 9.3.]

9.1.3 Persons who had pyrexia within 2 days after vaccination and those who had symptoms suggestive of allergy such as exanthema generalized

9.1.4 Persons with a history of convulsion

9.1.5 Those who have been diagnosed with immunodeficiency and those who have a close relative with congenital immunodeficiency

9.1.6 Person who may be allergic to any of the ingredients of this product

9.2 Persons with Renal Impairment

They are persons to be vaccinated with caution. [See 9.1.2.]

9.3 Persons with Hepatic Impairment

They are persons to be vaccinated with caution. [See 9.1.2.]

9.4 Patients with Reproductive Potential

Women of childbearing potential should be vaccinated after approximately 1 month of contraception in advance and advised to avoid becoming pregnant for approximately 2 months after vaccination.

9.5 Pregnant Women

This vaccine should not be administered to pregnant women. [See 2.5.]

9.6 Brest-feeding Women

The benefit associated with vaccination and the benefit of breast milk nutrients should be considered before continuing or discontinuing breast-feeding.

10. INTERACTIONS

10.1 Contraindications for Co-administration (Do not co-administer with the following.)

Drug name	Clinical symptoms and measures	Mechanism and risk factors
Corticosteroids Prednisolone, etc. Immunosuppressants Ciclosporin (Sandimmun) Tacrolimus (Prograf) Azathioprine (Imuran), etc. [See 2.4.]	This vaccine may cause smallpox-like symptoms.	Administration of this product may intensify or prolong the infection by the vaccine virus, because persons on immunosuppressive therapy, particularly those receiving long-term or high-dose treatment, or those discontinuing immunosuppressive therapy in the past 6 months may have compromised immune system.

10.2 Precautions for Co-administration (This drug should be administered with caution when co-administered with the following.)

Drug name	Clinical symptoms and measures	Mechanism and risk factors
Other live vaccines (injections) Measles vaccine Rubella vaccine Mumps vaccine Varicella vaccine BCG vaccine Yellow fever vaccine, etc. [See 7.2.]	This product should generally be administered at least 27 days after the administration of another live vaccine (injection)	Other live vaccines (injections) may interfere with the growth of this vaccine virus and subsequent immunity acquisition.

11. ADVERSE REACTIONS

The following adverse reactions may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.

11.1 Clinically Significant Adverse Reactions

11.1.1 Shock, anaphylaxis (incidence of both unknown)

Urticaria, dyspnoea, lip oedema, and laryngeal oedema may occur. [See 8.3.]

11.1.2 Convulsion (<0.1%)

Febrile convulsion may occur.

11.2 Other Adverse Reactions

	Incidence unknown
Hypersensitivity	Rash[Note)], dermatitis allergic, erythema multiforme
Local symptoms (Inoculation site)	Inoculation site reactions
Others	Pyrexia[Note)], axillary lymph nodes enlarged[Note)]

Note) It may occur around 10 days after vaccination.

14. PRECAUTIONS CONCERNING USE

****14.1 Storage of Vaccine before Reconstitution**

14.1.1 Refrigerated Storage

(1) This vaccine can be stored at 2 to 8°C for 2 years.

(2) Once the vaccine is moved to refrigerated storage, it should be used without being returned to frozen storage within the expiration period and within 2 years after being moved to refrigerated storage.

****14.2 Storage of Vaccine after Reconstitution**

14.2.1 This vaccine does not contain preservatives, and should therefore be used immediately. The solution remaining in the vial must always be disposed of at the end of the immunization session or within 6 hours whichever comes first, without being stored again and used for the next vaccination.

14.3 Precautions Concerning Administration of the Vaccine

**14.3.1 At inoculation

(1) A sterilized inoculation needle (bifurcated needle) should be used. The inoculation needle must be replaced for each vaccine recipient.

(2) This drug should not be mixed with other vaccines. [See 7.3.]

(3) Before reconstituting the vaccine, the container stopper and its surroundings should be disinfected using alcohol. After that, the vaccine should be homogeneously reconstituted with 0.5 mL of provided diluent. After reconstitution, the rubber stopper should be removed by cutting the metal cap. The tip of the bifurcated needle should be soaked in the solution, and vaccine solution appropriate for one recipient should be sucked out.

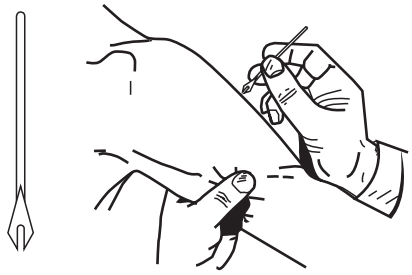
(4) In cases such as mass vaccination where a large number of persons need to be inoculated consecutively, approximately more than 250 recipients can be vaccinated if the 0.5 mL of vaccine solution is prepared by reconstituting this vaccine with 0.5 mL of provided diluent and bifurcated needles for smallpox vaccination with a single collection volume of 1 ± 0.5 μL (specified value) are used.

14.3.2 Inoculation site

In principle, the inoculation site should be within a diameter of approximately 5 mm on the origin area of deltoid muscle on the lateral upper arm. The site should be disinfected with a tightly wrung alcohol cotton and dried well. At 1 to 3 minutes after inoculation, any excess vaccine should be wiped off with a tightly wrung alcohol cotton.

14.3.3 Inoculation method

Multiple puncture technique: Hold a bifurcated needle perpendicular to the skin, rest the wrist of the hand holding the needle on the skin, and prick the skin by moving the wrist. Typically, a dedicated bifurcated needle to prick the skin 15 times (number of pricking as a guide). The skin should be pricked to the degree where blood will ooze from the skin.[2)] When using other bifurcated needles, consider their precautions for use before pricking the skin.



14.3.4 After inoculation

Medical examination should be performed between 10 and 14 days after inoculation to confirm the "take" (successful vaccination).

15. OTHER PRECAUTIONS

15.1 Information Based on Clinical Use

15.1.1 Autoinoculation (ectopic inoculation), in which a vaccine recipient touches the inoculation site by his/her hand after inoculation and vaccine viruses spread to other sites, has been reported.[1), 3)]

In addition, outside Japan, horizontal transmission of the virus has been reported from vaccine recipients to non-vaccine recipients after the administration of a live vaccine (injection) manufactured with a vaccinia virus strain different from the strain used in this product.

The vaccine recipient should avoid direct contact with the inoculation site and cleanse his/her hands and fingers thoroughly if he/she comes in contact with it.

**15.1.2 In the vaccines and immunization for monkeypox (mpox): Interim guidance issued by the WHO,[4)] it is recommended that the appropriate second- or third-generation smallpox vaccines within 4 days of exposure to mpox viruses (within 14 days in the absence of symptoms) should be administered.

17. CLINICAL STUDIES

17.1 Clinical Studies for Efficacy and Safety

17.1.1 Japanese clinical studies (children)

Approximately 50,000 children with primary vaccination, mainly 1 to 7 years old, were inoculated with this product. In 10,578 children with available detailed clinical symptom data, the "take" rate was 95.1%, the mean redness diameter (assessed on the 10^{th} day) was 18.4 mm, the mean induration diameter was 6.1 mm, the incidence of axillary lymph nodes enlarged was 12% to 19%, and the incidence of pyrexia (between the 4^{th} and 14^{th} days after inoculation) was 7.7%.

Observed symptoms included febrile convulsion in 3 children, eczema vaccinatum in 1 child, autoinoculation in 9 children (infection with the vaccinia virus resulting from the virus inoculation by hands from the local inoculation site to other sites), vaccinola (blisters and pustules around an inoculation site) in 28 children, and vaccinal eruption in 8 children (allergic eczema in the form of urticaria, in the form of erythema, and in other forms occurring around the 7^{th} to 10^{th} days after inoculation).

Usually, the maximum temperature of pyrexia ranged from 38°C to 38.9°C, which accounted for 77.4% of the children. The duration of the fever was 1 day in 60% of the children and up to 2 days in 85% of the children.

Regarding the indicators of the immune response, the HI antibody titer was $2^{3.3}$ (n=513) and the NT antibody titer was $4^{2.5}$ (n=97).

Electroencephalography performed in 56 children on the 14^{th} day after inoculation showed no abnormal findings.[1)]

17.2 Post-marketing Surveillance, etc.

17.2.1 Drug use-results survey in Japan (adults)

This product was administered to 268 adults. The "take" rate was 91.0% (94.4% after the primary vaccination, 81.7% after the secondary vaccination), the mean redness diameter was 23.8 mm (n =98), and the mean blister diameter was 7.6 mm (n=87). Observed adverse reactions included swollen lymph nodes in 19.4% (52/268 subjects), injection site erythema in 5.2% (14/268 subjects), pyrexia in 1.5% (4/268 subjects), malaise in 0.7% (2/268 subjects), postvaccination complication (satellite) in 0.7% (2/268 subjects), rash in 0.4% (1/268 subjects), injection site swelling in 0.4% (1/268 subjects), and post-vaccination autoinoculation (suspected ectopic inoculation) in 0.4% (1/268 subjects).

Regarding the indicators of immune response, the NT antibody titer was 37 (n=68) before inoculation and 1400 (n=39) 1 month after inoculation in adults given the primary vaccination, and 206 (n=30) before inoculation and 782 (n=12) 1 month after inoculation in adults given the secondary vaccination. These results showed a significant increase in the antibody titer. There were no adverse reactions related to the priority survey items, which included cardiac disorder (chest radiograph and ECG), encephalitis, and vaccinola/vaccinal eruption.[3)]

**18. PHARMACOLOGY

18.1 Mechanism of Action

It is considered that the smallpox virus and the mpox virus are transmitted through the airway via droplets from patients or by contact with skin lesions or body fluids of patients, and are proliferated in local lymph nodes. Then, by causing viremia, the virus is carried to the target organs in the whole body, leading to the onset of infection. When humoral and cellular immunity against the smallpox virus and mpox virus are acquired by inoculation of this product in advance, the proliferation of the infected virus is inhibited, thereby preventing onset.[5), 6), 7), 8), 9)]

18.2 Study to support Efficacy

This vaccine (2.5×10^5 PFU/case) or phosphate-buffered saline (PBS) as a negative control was administered to 14 cynomolgus monkeys or 6 cynomolgus monkeys, respectively, for a single percutaneous vaccination using a bifurcated needle. Sixty days after vaccination, 79 strains of mpox virus Zaire (5×10^7 PFU/case) were intravenously administered to these cynomolgus monkeys. After intravenous administration of the mpox viruses, in the negative control group, multiple skin lesions were observed on the entire body, and all the animals either died or were euthanized by 12 days after the administration of the mpox viruses. In the Vaccine group, crusts were formed by 12 days after the administration of the mpox viruses without deaths.[6)]

20. PRECAUTIONS FOR HANDLING

20.1 Do not store at −35°C or below because deterioration or damage of the rubber stopper could occur.

20.2 The virus of this product is vulnerable to sunlight and is rapidly inactivated. Exercise caution to avoid exposure to light both before and after reconstitution.

21. APPROVAL CONDITIONS

A risk management plan should be developed and implemented appropriately.

22. PACKAGING

Vaccine for 50 recipients or more: 1 vial
(Diluent 0.5 mL 1 vial is co-packed)

23. REFERENCES

1) Masayoshi Yamaguchi, et al.: Ministry of Health and Welfare Special Research, Clinical Virology 3(3), 1975: 53-63
2) Tuberculosis and Infectious Diseases Control Division, Health Service Bureau, MHLW: Smallpox Handling Guidelines (Version 5), May 14, 2004, 84-85
3) Ichiro Kurane, et al.: Research into the safety, efficacy, and productivity of cell cultured live attenuated smallpox vaccine, 2010 General Overview/Report for Assigned Research, 2010: 35-38
4) WHO. Vaccines and immunization for monkeypox: Interim guidance, 16 November 2022
5) Edited by National Institute of Health Alumni Association: National Institute of Health Alumni Association. National Institute of Health Alumni Association Journal: Japanese Vaccine, 2nd Edition, 1977: 1-26
6) Gordon SN, et al.:J Infect Dis. 2011;203(8):1043-1053.
7) Saijo M, et al.:J Virol. 2006;80(11):5179-5188.
8) Iizuka I, et al.:Jpn J Infect Dis. 2017;70(4):408-415.
9) Kennedy JS, et al.:J Infect Dis. 2011;204(9):1395-1402.

24. REFERENCE REQUEST AND CONTACT INFORMATION

KM Biologics Co., Ltd. Drug Information
1-6-1 Okubo, Kita-ku, Kumamoto-shi, Kumamoto 860-8568, Japan
Toll free number 0120-345-724

25. PRECAUTION CONCERNING HEALTH INSURANCE BENEFITS

This drug is not covered by insurance (not listed in the Japanese National Health Insurance [NHI] price list).

26. MARKETING AUTHORIZATION HOLDER, etc.

26.1 Marketing Authorization Holder

KM Biologics Co., Ltd.
1-6-1 Okubo, Kita-ku, Kumamoto-shi, Kumamoto, Japan

Attention

This document is prepared in Aug 2024 on the basis of the Japanese text current at that time.
This document might differ from the Japanese Package Insert.