LC16m8 Attenuated Smallpox Vaccine

History of Development of LC16m8

As the WHO worldwide eradication campaign proceeded, concerns surrounding the adverse event profile of traditional smallpox vaccines rose among the health authorities of countries with a low incidence of disease. In response to this, Japan formed the Smallpox Vaccines Research Group (SVRG), which was charged with identifying a safer smallpox vaccine for use in routine immunization. Work done by So Hashizume at the Chiba Serum Institute identified the LC16m8 strain of vaccinia as a potentially safer strain for use in Japan. This vaccine was then studied in extensive clinical trials by the SVRG and was subsequently licensed in Japan.

Characteristics of LC16m8

Lister-derived, replicating, attenuated strain

LC16m8 was derived from the Lister strain of vaccinia by passaging multiple times, with selection for an attenuated phenotype (1). In contrast to replication-deficient vaccines such as Modified Vaccinia Ankara (MVA), LC16m8 retains the majority of the vaccinia genome (2) and is capable of replication at the site of inoculation, hence producing a “take” lesion in vaccinees.

Production method and dosage form

LC16m8 is produced in cell culture using primary rabbit kidney cells as the cell substrate. A lyophilized, multi-dose vial configuration is used. Real-time data from the US clinical trial supplies shows the vaccine (bulk and final vial) to be stable for at least 12 months under routine storage conditions, and also stable for at least 30 days post-reconstitution when refrigerated or stored at room temperature. Although LC16m8 was initially manufactured by the Chiba Serum Institute, in 2002 this institute was dissolved, and the Japanese government selected The Chemo-Sero-Therapeutic Research Institute (also referred to as KAKETSUKEN) of Kumamoto, Japan, to take over production of LC16m8.

LC16m8 Safety and Efficacy Data

LC16m8 is administered as a single dose using the traditional scarification method. During the 1974-75 timeframe, the SVRG conducted studies of 50,000 children who received LC16m8. A total of 9,538 were followed closely. Take rates of 95% were recorded. Low fever rates of 7.8% were reported, no encephalitis was seen, and one case of eczema vaccinatum occurred. This led to the conclusion that LC16m8 was a safer vaccine, and consequently it was licensed. In a recent clinical study conducted in the US by VaxGen, 100% take rates and seroconversion were noted in the LC16m8 recipients. Comprehensive cardiac monitoring was performed, and no evidence of myopericarditis was noted. The vaccine was generally well tolerated.

Several animal studies examining the protective efficacy of LC16m8 as well as its safety profile have been conducted, with favorable results. The neurovirulence of LC16m8 is lower than that seen with traditional unattenuated vaccines (1), and animal challenge studies using various orthopoxviruses demonstrate protective efficacy (2, 3, 4).

Regulatory Status of LC16m8

The Chiba Serum Institute was issued a conditional license in 1975, with an unconditional license following in 1980 according to the procedures of the Japanese regulatory authorities. KAKETSUKEN was licensed to produce LC16m8 in 2003.

VaxGen, Inc. holds an active IND for the study of LC16m8 in the USA. VaxGen has exclusive first refusal rights to market LC16m8 outside Asia and holds exclusive rights to LC16m8 within the US.

Availability of LC16m8

KAKETSUKEN currently manufactures LC16m8 for the Japanese national stockpile. The existing licensed bulk production facility has an annual capacity of approximately 30M doses. A new bulk facility, constructed according to current GMP standards, will be available shortly with an annual capacity of approximately 80M doses.

References

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