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NEXIPOX®

Varicella Vaccine With Trehalose

Made For India

(Varicella Vaccine, Live, I.P. Freeze-dried)

Oka Strain (VR 795) - ATCC

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Next Generation Varicella Vaccine

Powered with `WHO´ recommended TREHALOSE

Novo Medi Sciences has vaccinated more than 4.9 million beneficiaries against chickenpox

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Varicella Vaccine With Trehalose

Made For India

World's Only Thermostable Varicella vaccine

- 0 0% Breakthrough Rate
- 1 100% Antigenic Delivery
- 2 2 Age Groups : Paediatrics & Adults
- 3 3 Years Shelf Life
- 4 4.9 Million Doses

Contents

Chickenpox - Clinical Features and Management

Introduction: Varicella-Zoster Virus (VZV) is a ubiquitous human alphaherpesvirus, which causes Varicella (Chickenpox) and Herpes zoster (Shingles). Chickenpox results from primary VZV infection. It is a common childhood illness associated with fever and a generalized pruritic vesicular rash and is also seen in adults in tropical countries like India.

As is a characteristic of the alphaherpesviruses, VZV establishes latency in cells of the dorsal root ganglia after primary infection. Herpes zoster presents with localized, painful, vesicular rash involving one or adjacent dermatomes and is caused by VZV reactivation. The incidence of Herpes zoster increases with age due to immunosenescence or immunosuppression.

Historically, the relationship between the etiologies of varicella and herpes zoster was first suggested by Von Bokay in 1892, from the observation that young children often developed varicella after exposure to an adult with herpes zoster.[1]

Clinical Features: Primary chickenpox infection is characterized by a relatively long incubation period, ranging from 10 to 21 days, with the usual duration being 14 to 16 days. About half of the cases begin with a prodrome of fever, malaise, headache and abdominal pain. Prodromal symptoms last about 24 to 48 hours before the first skin lesions appear and are more common in older children and adults.

The initial skin lesions of chickenpox often involve the scalp, face or trunk and are pruritic, erythematous macules. The maculopapular phase evolves to a vesicular phase, during which small, fluid-filled vesicles appear in existing or new erythematous lesions.

New skin lesions appear in most children for 3 to 5 days with several 'crops' of new lesion formation. The varicella rash is more extensive in older children and in secondary household, contacts are at risk of contracting the disease. Presence of various forms of rash at the same time also called as pleomorphic rash is the hallmark of chickenpox infection.

The crusting phase begins with clouding of the vesicular fluid, within about 24 to 48 hours after the appearance of each lesion.[2]

Complications of Chickenpox: The most common varicella-related complication in otherwise healthy children is secondary bacterial infection of the skin rash, usually due to Staphylococcus aureus or Streptococcus pyogenes (Group A beta-hemolytic Streptococcus). Other manifestations include staphylococcal or streptococcal pneumonia, arthritis or osteomyelitis.[2]

Varicella appears to lead to transient hepatitis in most children. The differential diagnosis of varicella hepatitis is Reye's syndrome, a non-inflammatory acute encephalopathy with fatty degeneration of the liver, characterized by vomiting, increased intracranial pressure and progressive neurologic deterioration. Children with varicella should not be given aspirin, because it increases the risk of developing Reye's syndrome.

Increased morbidity and mortality associated with varicella in adults is primarily due to the higher risk of varicella pneumonia in these patients.

Neurologic complications are the second most frequent reason for hospitalization of children with chickenpox. Meningoencephalitis and cerebellar ataxia are the major clinical manifestations of central nervous system involvement [3]. Central nervous system complications are most common in patients younger than 5 years and older than 20 years.

Hemorrhagic complications are rare in healthy children with varicella, but adults are at higher risk. Thrombocytopenia during acute varicella is associated with bleeding into skin lesions, petechiae, purpura, epistaxis, hematuria and gastrointestinal hemorrhage. Immune compromised children are prone to progressive varicella infection as well as hemorrhagic varicella.

In general, chickenpox disease is more severe in adults than in children. The mortality caused by chickenpox in healthy children is 2 per 100,000 cases, in healthy infants is 8 per 100,000 cases, in healthy adults is 25 per 100,000 cases, in immune compromised patients is 10-20% and is 20-30% in neonatal varicella where the mother develops chickenpox 5 days before or 2 days after delivery.

Herpes zoster: VZV infection of cells in the dorsal root ganglia is probably a consequence of all primary VZV infections.[4, 5, 6] Herpes zoster, the symptomatic VZV reactivation, causes a vesicular rash with large, fluid-filled lesions and acute neuritic pain, usually involving the dermatomal distribution of a single sensory nerve.[1] The rash is often preceded by several days of localized neuropathic pain.

The most common and debilitating complication of Herpes zoster is Post-Herpetic Neuralgia (PHN). The risk of prolonged PHN is as high as 40 to 50% in individuals older than 60 years.[7]

Management of Chickenpox: Acyclovir, famciclovir and valacyclovir are the antiviral drugs effective in the treatment of VZV infections in patients with malignancy, bone marrow or organ transplantation, high-dose steroid therapy, congenital T-cell immunodeficiency, HIV infection, neonatal varicella after maternal varicella beginning within 5 days before or 2 days after delivery and associated pneumonia or encephalitis.

Antiviral therapy does not eliminate VZV from the host, so further episodes of reactivation can occur when treatment is stopped.[2]

Prevention of Chickenpox: VZV transmission to susceptible individuals is generally difficult to prevent because infected persons are contagious for 24 to 48 hours before the clinical signs of chickenpox are obvious.[8]

Passive Antibody Prophylaxis with VZIG, a high-titer preparation of VZV IgG antibodies, is indicated for susceptible high-risk individuals, including immunocompromised children with no history of varicella, pregnant women who have had a close exposure to an individual with varicella or herpes zoster and newborn infants exposed to perinatal maternal varicella.

Chickenpox Vaccine: The live attenuated varicella vaccine, made from the Oka strain, is the first human herpes virus vaccine that has been licensed for clinical use in several countries, including India.

Immunological studies of vaccine recipients given the live attenuated varicella vaccine have demonstrated consistently high seroconversion rates (above 95%), as well as persistence of VZV IgG antibodies 1 year after immunization. The vaccine also elicits T-lymphocytes that recognize VZV antigens or purified viral proteins.[9] Effective induction of persistent memory T-lymphocyte responses to VZV is important since cell-mediated immunity is fundamental to the host response to natural VZV infection.[10]

It is necessary to give two doses of vaccine, separated by at least 4 weeks, to achieve seroconversion rates of more than 95% in susceptible adults.[11]

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Varicella Zoster Vaccine

Varicella Zoster Virus (VZV) was the first herpes virus isolated and propagated in cell culture. The wild-type Oka strain (Parent Oka; P-Oka) was attenuated through cell culture passage by Takahashi in 1974, who described the efficacy of this Oka-derived virus (V-Oka) as a vaccine. After 15 years of experience in clinical trials, the live attenuated varicella vaccine was licensed in the United States in 1995 and now V-Oka vaccines are available in many countries.[1] Routine universal immunization, instituted in 1995, has had a major impact on varicella incidence, hospitalizations and deaths in the United States.[2]

The two major challenges in developing the varicella vaccine were how to attenuate the virus so that its inoculation did not cause varicella and how to address the neurotropism of VZV. The wild-type Oka strain was attenuated using the empiric approach of growth in non-human cells, taking advantage of the fact that VZV replicates in guinea pig embryo fibroblasts. After 11 passages in human lung fibroblasts, P-Oka was passed 6 times in guinea pig cells and transferred back to human lung fibroblasts to create V-Oka stocks.

Investigations in the SCIDhu mouse model (Severe Combined Immune Deficient mouse with Human xenograft) of VZV pathogenesis indicate that vaccine Oka attenuation is related to reduced growth in skin whereas infectivity for T cells and dorsal root ganglia is not different from parent Oka.[1,3,4]

Subcutaneous inoculation of V-Oka did not cause illness in children, indicating that viremia did not occur or was subclinical and seroconversion was elicited reliably.

The pre-licensure clinical experience in the United States has demonstrated that 1000-3000 PFU or more of V-Oka elicits adaptive immunity when administered subcutaneously to healthy children.[5] One dose was shown to induce humoral and cell-mediated immunity in more than 95% of vaccine recipients. Immunization with varicella vaccine has elicited IgG antibodies as well as VZV-specific helper and cytotoxic T cell responses directed against the major viral glycoproteins and the immediate early transactivating protein IE62.[1]

Immunology

Although both VZV antibodies and VZV-specific T cells are induced, cell-mediated immunity is necessary to resolve primary VZV infection.[1] Adaptive CD4 and CD8 T cells that recognize VZV proteins persist in the healthy host, along with VZV IgG antibodies that have neutralizing function. Memory immunity to VZV may be determined by the initial expansion of VZV T cells or by secondary stimulation related to varicella exposures or sub-clinical reactivations, or by all three mechanisms.[6] Symptomatic second episodes of varicella are rare but the risk of herpes zoster in older adults and immunocompromised patients correlate with reduced T cell proliferation and

interferon γ production by peripheral blood mononuclear cells stimulated with VZV and fewer VZV-specific CD4 T cells. When VZV reactivates to cause herpes zoster, VZV-specific T cells undergo a substantial and sustained expansion.[7]

Fluorescent Antibody to Membrane Antigen (FAMA) assay was the method used extensively in pre-licensure studies on varicella vaccine. Measurement of FAMA provides a quick and simple serologic means of determining immunity to varicella. It is ideally suited for rapid determination of the immune status for serologic surveys since only a small quantity of serum is required and large numbers of specimens can be processed simultaneously in micro titer plates. The test for VZV FAMA is specific and sensitive. No cross-reactions with other closely related herpes viruses have been found.[9]

Other types of assay are ELISA, glycoprotein-based ELISA (gpELISA) and in vitro neutralization assays. The ELISA is not as sensitive as the gpELISA. The FAMA assay is less sensitive but more specific than either ELISA, hence more accepted.[5]

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Safety of Gelatin Free Formulation

Sr. No.	Author	Test Vaccine	No. of Subjects (years)	Immunogenicity	Adverse Reactions	Conclusion
1.	SUN Hui-lai et al (2009)	Freeze-dried live attenuated vaccine BCHT Biotechnology Co. Ltd.	Phase 1: 60 subjects age 12 & above (n=20), age 6 ~ 12 (n=20) Phase 2: 400 subjects age 1~5 (n=200), age 6~12 (n=200)	Antibody Positive Seroconversion Rate-98.31% Antibody GMT Pre-vaccination-1:3:3.86 Antibody GMT Post vaccination-1:147.38	Local reaction-5.25% Systemic reaction-12%	Test vaccine showed good immunogenicity and safety
2.	JIANG Zhenggang etal (2009)	Lyophilized Live attenuated varicella vaccine BCHT Biotechnology Co. Ltd.	Phase 1: 60 subjects age 12 & above (n=20), age 6 ~ 12 (n=20) Phase 2: 400 subjects age 1~5 (n=200), age 6~12 (n=200)	-NA-	2.7%, 4.7%, 4.8%, 2.3%, 2.3% & 0.3% after 4h, 24h, 48h and 72h, respectively, no side effect was observed after six weeks.	Test varicella vaccine possessed good safety and is worth popularizing
3.	CHEN - Enfu et al (2009)	Varicella vaccine BCHT Biotechnology Co. Ltd.	785 Children aged 1~2, and 345 aged 3~13	Seroconversion rate of successful immunization was 98.3% GMT before and after VarV immunization was 1:4.7 and 1:163.2 respectively	2.29%, 3.69%, 3.82%, 1.78% and 0.25% after 30min, 4h, 24h, 48h and 72h respectively, no side effects after six weeks.	Live attenuated domestic varicella vaccine showed good safety and immunogenicity
4	LI Yong-Cheng et al (2012)	Freeze-dried live attenuated varicella vaccine BCHT Biotechnology Co. Ltd.	7546 subjects, 4040 male (53.54%) 3506 Female (46.46%)	-NA-	Local reactions - 16/7546 (0.21%) Systemic reaction - 521/7546 (6.90%) 3 Cases of both local (swelling) and general (fever) reactions	The adverse reaction rate of Test vaccine was not more than those reported by other researchers in China & no severe reactions were observed, indicating high safety of the vaccine

Safety of Gelatin Free Formulation

Sr. No.	Author	Test Vaccine	No. of Subjects	Immunogenicity	Adverse Reactions	Conclusion
5.	Lu Zhi - hui et al (2013)	Gelatin-free freeze-dried live attenuated varicella vaccine BCHT Biotechnology Co. Ltd.	47103 subjects 1 year old - 36696 2 year old - 6230 3 year old - 1944 4 year old & above - 2233	-NA-	Allergic reactions - 16 General reactions - 5 No adverse reactions seen in children 4 year old & above	Results suggest that the gelatin-free freeze-dried live attenuated varicella vaccine is safe

Comparative Studies with Gelatin Free Formulation and that with Gelatin (Study 8)

Sr. No.	Author	Test Vaccine	Control Vaccine	No. of Subjects		Immunogenicity		Adverse Reactions		Conclusion
				Test grp	Control grp	Test grp	Control grp	Test grp	Control grp	
6.	BAI Yun-hua et al (2011)	Gelatin-free freeze-dried live attenuated varicella vaccine, BCHT Biotechnology Co. Ltd.	Gelatin containing freeze-dried live attenuated varicella vaccine, BCHT Biotechnology Co. Ltd.	1~5 years - 302 subjects, 6~12 years - 394 subjects	1~5 years - 310 subjects, 6~12 years - 392 subjects	1~5 years GMT Pre-immunization 1:4.11 GMT Pre-immunization 1:58.49 Seroconversion rate 98.70% 6~12 years GMT Pre-immunization 1:7.52 GMT Post-Immunization 1:121.08 Seroconversion rate 99.06%	1~5 years GMT Pre-immunizaation 1:3.95 GMT Pre-immunizaation 1:64.28 Seroconversion rate 98.74% 6~12 years GMT Pre-immunization 1:8.35 GMT Post-immunization 1:126.73 Seroconversion rate 98.08%	Systemic reaction incidence was 11.49% (80/696) Moderate fever was 0.57 (4/696) & total local reaction incidence 3.02% (21/696)	Systemic reaction incidence was 14.96% (105/702) Moderate fever was 1.71 (12/702) & total local reaction incidence 2.99% (21/702)	Immunogenicity of gelatin-free freeze-dried live attenuated varicella vaccine was equivalent to that of gelatin-containing vaccine, while the moderate fever rate decreased significantly

Sr. No.	Author	Test Vaccine	Control Vaccine	No. of Subjects		Immunogenicity		Adverse Reactions		Conclusion
				Test grp	Control grp	Test grp	Control grp	Test grp	Control grp	
7.	TANG Yan et al (2012)	Gelatin-free freeze-dried live attenuated varicella vaccine BCHT Biotechnology Co. Ltd.	Freeze-dried live attenuated varicella vaccine GlaxoSmithKline (GSK)	Age group 1~5 years - 277 subjects, 132 male & 145 females age group 6~12- 252 subjects, 135 males & 117 females	Age group 1~5-277 subjects, 148 male & 129 females age group 6~12- 244 subjects, 127 males & 117females	Antibody GMT Pre-immunization 1:12.1384 Antibody GMT Post-immunization 1:126.3431 Seroconversion rate 96.99%	Antibody GMT Pre-immunization 1:13.3579 Antibody GMT Post-immunization 1:140.2712 Seroconversion rate 96.98%	Incidence of adverse reactions 10.96% (58/529) Systemic reactions 6.62% (35/529) Local reactions 4.35% (23/529)	Incidence of adverse reactions 17.66% (92/521) Systemic reactions 8.06% (42/521) Local reactions 9.60% (50/521)	Test vaccine had equivalent immunogenicity but higher safety by reducing the incidence of adverse reactions
8.	BIAN Guo-lin et al (2012)	Freeze-dried live attenuated varicella vaccine BCHT Biotechnology Co. Ltd.	Freeze-dried live attenuated varicella vaccine GlaxoSmithKline (GSK)	7~13 years - 60 children	7~13 years - 58 children	Antibody GMT Pre-immunization 1:5.44 Antibody GMT Post-immunization 1:205.54	Antibody GMT Pre-immunization 1:7.14 Antibody GMT Post-immunization 1:203.98	No systemic or local reactions	No systemic reactions Local reactions 2/58 subjects (3.44%)	Domestic and imported Varicella vaccines had good safety and immunogenicity

The Evidence On NEXIPOX® - Published Clinical Trials

Detailed summary of published clinical trials is provided in the next few pages. Over 14,000 subjects were part of these studies. In addition, there was also a post marketing study on 47,000 subjects. VZV antibody titers in the serum were assayed by means of Fluorescent-Antibody-to-Membrane-Antigen (FAMA). A subject with a fourfold increase in titre from baseline was considered to be seroconverted. The vaccine provided seroconversion in majority (>95%) of the subjects and the rate of seroconversion was comparable to other marketed vaccines. It was also well tolerated, most of the side effects being local. Interestingly, the gelatin free formulation showed lesser adverse reactions compared to the earlier formulation with gelatin as well as other marketed vaccines with gelatin.

Non Comparative Studies on Immunogenicity and Safety

1. SUN Hui-lai, FANG Han-hua, LI Rong-cheng. Adverse Reaction and Immunogenicity Induced by Freeze-dried Live Attenuated Varicella Vaccine Chinese Journal of Biologicals. (2009); 22:702-704.

In this study, 460 subjects aged above 1 year from Guilin City, Yongfu County were administered freeze-dried live attenuated varicella vaccine manufactured by Changchun BCHT Biotechnology Co. Ltd.

Out of these, 60 subjects selected for phase I trial were assigned to three groups: aged 1-5 years (n=20), aged 6-12 years (n=20) & adult group 12 years & above (n=20). The other 400 subjects for phase II were divided into two groups: aged 1-5 years (n=200) and aged 6-12 years (n=200).

The adverse reactions in the trial were assessed according to Guidance for the Grade Standards of Adverse Reactions in Clinical Trial for Preventive Vaccine [promulgated by SFDA (State Food Drug Administration) on October 14, 2005]. General adverse reactions and abnormal reactions were assessed 30min, 6h, 24h, 48h, 72h and 4-10 days after immunization in phase I and II. The adverse reactions within 30 days were collected through telephone interview including those reported by subjects themselves.

Blood samples were obtained from the subjects, both pre-vaccination and at 4th to 6th weeks post-vaccination. VZV antibody response in the blood serum was assayed by means of Fluorescent-Antibody-to-Membrane-Antigen (FAMA).

No severe local and / or systemic adverse reactions were observed in 60 subjects of phase I during 30-day observation period.

The incidence of general or local adverse reactions within the 10-days observation period following vaccination in phase II subjects in 1-5 years and 6-12 years age groups are summarized in the following table:

Age Group (Years)	No. of Subjects	Redness n (%)	Swelling n (%)	Pain n (%)	Itchiness n (%)	Total n (%)
1-5	200	2 (1)	3 (1.5)	0	5 (2.5)	10 (5)
6-12	200	3 (1.5)	2 (1)	4 (2)	2 (1)	11 (5.5)
Total	400	5 (1.25)	5 (1.25)	4 (1)	7 (1.75)	21 (5.25)

Total incidence of fever in the two groups (1-5 years and 6-12 years) was 13.50% and 10.50% respectively and the difference had no statistical significance ($\chi 2$ =0.8523, P = 0.3552). Further, all subjects with fever were clinically diagnosed as influenza and not related to vaccination.

The Seroconversion Rate was 98.31%. The GMT of antibody after immunization was 147.38, compared to 3.86 before immunization. The GMT of antibody after immunization was significantly higher in subjects aged 6-12 years (190.31) than that in aged 1-5 years (112.26).

The study concluded that BCHT freeze-dried live attenuated varicella vaccine showed good safety and immunogenicity.

2. JIANG Zheng-gang, CHEN En-fu, LI Qian, et al. Observation on Side Effect of the Domestic Lyophilized Live Attenuated Varicella Vaccine. Zhejiang Journal of Preventive Medicine. 2009; 21:12-13.

A study to evaluate safety of the domestic lyophilized live attenuated varicella vaccine manufactured by Changchun BCHT Biotechnology Co. Ltd. was conducted by the Center for Disease Control and Prevention of Zhejiang Province.

617 subjects, including 439 children aged 12 months-36 months and 178, aged 37 months-13 years were observed for side effects after 30min, 4h, 24h, 48h, 72h and 6 weeks of vaccination. The results showed that 2.7 %, 4.7 %, 4.8 %, 2.3% and 0.3 % of the children had side effect at different times as above and no side effect was observed after six weeks.

A total of 29 children (4.7%) had fever, including 23 (3.7%) with mild fever and remaining 1% with moderate to high fever. Other adverse reactions reported were headache, local swelling and induration.

No severe side effect was observed during the study and it was concluded that domestic lyophilized live attenuated varicella vaccine possessed good safety.

3. CHEN Enfu, JIANG Zheng-gang, LI Qian, et al. Safety and Immunogenicity of Lyophilized Live Attenuated Domestic Varicella Vaccine. Chinese Journal of Vaccines and Immunization. 2009; 15: 435-437.

A study was conducted to evaluate the safety and immunogenicity of Varicella vaccine (Oka strain), which was cultured and prepared using MRC-5 human diploid cells as recommended by WHO.

A total of 785 subjects, of which 440 were aged 1-2 years and 345 aged 3-13 years, were monitored for adverse reactions at 30min, 4h, 24h, 48h, 72h and 6 weeks after vaccination.

Antibodies against varicella were detected by Fluorescent Antibody to Membrane Antigen (FAMA) method in 177 children.

It was observed that 3.69 %, 3.82 %, 1.78% and 0.25 % of the subjects had side effect after 4 hours.

Age Group (Years)	No. of Subjects	Pre-vaccination GMT	Post-vaccination GMT	Seroconversion rate (%)
1-2	52	1:4.10	1:121.40	96.2
3-13	125	1:5.00	1:184.60	99.2
Total	177	1:4.70	1:163.20	98.3

It was concluded that no severe side effect was observed in the study and the seroconversion rate was higher than that reported in other studies on domestic vaccine.

4. LI Yong-cheng,GAO Zhi-gang,TAO Hang. Safety of Freeze-Dried Live Attenuated Varicella Vaccine. Chinese Journal of Biologicals. 2012; 25:1667-1670.

In this study, the safety of freeze-dried live attenuated varicella vaccine manufactured by Changchun BCHT Biotechnology Co. Ltd. was assessed in 7546 subjects of which 4040 were males (53.54%) and 3506 were females (46.46%). The age distribution of these children was: 2821 infants (1-3 years old) (37.38%), 2036 pre-schooler (4-6 years old) (26.98%) and 2689 school-going children (7-12 years old) (35.63%).

534 (7.08%) cases of adverse reactions to vaccination were observed. These included 16 cases of local reactions, 521 cases of systemic reactions and 3 cases of both local (swelling) and general (fever) reactions.

In the 16 cases of local reactions, 9% cases had swelling and 7% cases had induration.

Amongst the 521 cases of systemic reactions, 478 cases had fever, 22% cases had allergic rash, and others side effects like dizziness and weakness, diarrhea, nausea and vomiting, sleepiness, headache, stomach ache, coughing, etc.

The difference in adverse reaction incidences among the three age groups (infant, pre-schooler and school-going children) had no statistical significance (P>0.05).

It was concluded that freeze-dried live attenuated varicella vaccine demonstrated good safety.

Safety of Gelatin Free Formulation

5. LU Zhi-hui, LU Zhi-min, CHEN Guang-z hong, et al. Observation and Analysis on the Safety of a Gelatin-free Freeze-dried Live Attenuated Varicella Vaccine. Practical Preventive Medicine. 2013; 20:1449-1451.

A study evaluated the safety of gelatin-free freeze-dried live attenuated varicella vaccine in 47103 subjects aged 1 year and above.

The adverse reactions of vaccinated subjects were monitored face-to-face or by telephonic interview after 30min, 6h, 24h, 48h, 72h and 4-10 days of the inoculation. Meanwhile, professional staff informed the subjects or their guardians to monitor their health by sending the Health Notification. If any adverse reaction occurred, the subject informed the vaccination organization immediately, and the professional staff verified the information. The observation period ended 10 days after the vaccination.

A total of 21 cases of adverse reaction were found, including 5 cases of fever and 16 cases of allergic

reaction. No adverse reaction was reported in the subjects 4 years old and above.

The incidence of adverse reactions was 4.46/10,000 without statistically significant difference compared to the incidence of 3.24/10,000 after inoculation of freeze dried live attenuated varicella vaccine containing gelatin as reported earlier.

Most of the adverse symptoms occurred in 24h after the inoculation of the test vaccine. No serious adverse reaction was observed and all cases were mild, showing the high safety of gelatin-free freeze-dried live attenuated varicella vaccine.

Comparative Studies – Gelatin Free Formulation

6. BAI Yun-hua, YANG Li-qing, GUO Li-shu et al. Safety and Immunogenicity of Gelatin-free Freeze-dried Live Attenuated Varicella Vaccine. Chinese Journal of Biologicals. 2011; 24:1336-42.

Most of the anaphylaxis reactions caused by vaccination are reportedly related to gelatin or its hydrolysis peptide fragments derived from animals that are usually used as stabilizer in vaccines. In addition, gelatin derived from cattle or pig has the potential risk of spreading animal derived viruses leading to infections such as Human Spongiform Encephalopathy.

This study was carried out to observe safety and immunogenicity of Gelatin-free Freeze-dried Live Attenuated Varicella Vaccine produced by Changchun BCHT Biotechnology Co. Ltd.

1398 subjects of 1-12 years of age were included in this study. 612 children were 1-5 years old of which 302 were in test group (157 males and 145 females) and 310 in control group (158 males and 152 females). 786 children were 6-12 years-old of which 394 were in test group (212 males and 182 females) and 392 in control group (211 males and 181 females).

The test group received Gelatin-free Freeze-dried Live Attenuated Varicella Vaccine and the control group received Freeze-dried Live Attenuated Varicella Vaccine containing gelatin, both manufactured by BCHT.

Systemic adverse reactions such as fever, cough, fatigue, headache, allergy, vomiting and myalgia were seen in 80/696 (1.49%) children in test group as against 105/702 (14.96%) children in control group.

Except for incidence of moderate fever in test group that was obviously lower than that of control group ($P<0.05$), the difference in other systemic and local adverse reactions between the two groups was not statistically significant.

Pain was the main local reaction observed in both test and control group. Other local reactions seen in less than 1% subjects were mainly redness, swelling, pruritus and skin eruption.

The antibody GMT levels were assessed by means of Fluorescent-Antibody-to-Membrane-Antigen (FAMA) method in 733 subjects. The results are as below:

Age (Years)	No. of Subjects	Pre-inoculating GMT	Post-inoculating GMT	Seroconversion rate (%)
1-5				
Test Group	154	1:4.11	1:58.49	98.70
Control Group	159	1:3.95	1:64.28	98.74
6-12				
Test Group	212	1:7.52	1:121.08	99.06
Control Group	208	1:8.35	1:126.73	98.08

In conclusion, the gelatin-free live attenuated varicella vaccine was shown to have equally good safety and immunogenicity as the live attenuated varicella vaccine containing gelatin but with significantly less incidence of moderate fever.

5 Years PMS

7. TANG Yan, SU Jia-li, XIA Yan-hui et al. Safety and Immunogenicity of Domestic Gelatin-Free Freeze-Dried Live Attenuated Varicella Vaccine. Chinese Journal of Biologicals. 2012; 25:1516-1519.

In a study to evaluate the safety and immunogenicity gelatin-free freeze-dried live attenuated varicella vaccine manufactured by Changchun BCHT Biotechnology Co. Ltd. (test group) in comparison to the freeze-dried live attenuated varicella vaccine (Varilrix) manufactured by Glaxo SmithKline Biologicals S. A. (control group).

The 1050 subjects included 554 children in age group 1-5 years comprising test group of 277

subjects (132 males and 145 females) and control group of 277 subjects (148 males and 129 females). The other group of 6-12 years-old had 496 children comprising test group of 252 subjects (135 males and 117 females) and control group of 244 subjects (127 males and 117 females).

In the 14 days of active observation period after vaccination, the incidence of adverse reactions was 10.96% (58/529) and 17.66% (92/521) for the test group and control group, respectively. The test group showed better safety than control group as the difference between two groups had statistical significance ($\chi 2 = 9.6063, P = 0.0019$).

The incidence of systemic adverse reactions - mainly fever - was 6.62% (35/529) and 8.06% (42/521) for the test group and control group, respectively with the difference between two groups having no statistical significance.

The incidence of local adverse reactions, mainly pain and pruritus, was 4.35% (23/529) and 9.60% (50/521) for the test group and control group, respectively. The difference between the two groups was statistically significant ($\chi 2 = 11.1798, P = 0.0008$).

Blood sample was collected from 531 subjects before and 6 weeks post-vaccination and results of antibody testing by Fluorescent Antibody to Membrane Antigen (FAMA) method are summarized below:

Group	No. of Subjects	Pre-vaccination GMT	Post-vaccination GMT	Seroconversion rate (%)
Test Group	529	1:12.1384	1:126.3431	96.99%
Control Group	521	1:13.3579	1:140.2712	96.98%

The study showed that the incidence of adverse reactions, mainly local adverse reactions, was statistically lower in test group when compared with that of the control group while both the vaccines had equivalent immunogenicity.

8. BIAN Guo-lin, TANG Xue-wen, SHI Hong-hui, et al. Study on Safety and Immunogenicity of Imported and Domestic Varicella Attenuated Live Vaccine (Freeze-Dried) for Children. Chinese Journal of Vaccines and Immunization. 2012; 18: 435-437.

This study evaluated the safety and immunogenicity of domestic Varicella vaccine manufactured by Changchun BCHT Biotechnology Co. Ltd. and imported Varicella vaccine manufactured by GlaxoSmithKline (GSK) in 118 children aged 7-13 years old, 60 in domestic and 58 in imported vaccine group.

Physicians monitored the adverse reactions during 10 days after the vaccination. Sample of 2ml venous blood was collected from subjects before and 6 weeks post vaccination. Antibodies were detected by Fluorescent Antibody to Membrane Antigen (FAMA) method.

There were no systemic or local reactions observed in the domestic vaccine group. No systemic reaction but two local reactions, i.e., swelling was observed in the imported vaccine group.

The results of immunogenicity testing are given in the table below:

Group	No. of Subjects	Pre-vaccination GMT	Post-vaccination GMT	Seroconversion rate (%)
Domestic Vaccine Group	60	1:5.44	1:205.44	100
Imported Vaccine Group	58	1:7.14	1:203.98	100

The study concluded that both domestic and imported Varicella vaccines were safe and immunogenic in children.

Published Indian Clinical Trial

ZHU Chang-lin, ZHAO Zhen-yi, TAO Hang, XU Na, WU Jin-chang, Safety and immunogenicity of freeze-dried live attenuated varicella vaccine in India, Chinese Journal of Biologicals. 2015; 28:711-714.

A multicentric, single-blind, phase III clinical trial to evaluate the safety and immunogenicity of freeze-dried live attenuated varicella vaccine manufactured by BCHT Biotechnology Co. Ltd. was carried out in comparison with freeze-dried live attenuated varicella vaccine (Varilrix) manufactured by GlaxoSmithKline (GSK) used as the control vaccine.

104 healthy children between ages of 1-2 years without history of chickenpox, vaccination history of varicella vaccine or contraindication to vaccination were selected to receive either the test vaccine or control vaccine.

Trial was carried out at Dr. D. Y. Patil Hospital & Research Centre, Aadithya Adhikari Hospital, Bharati Vidyapeeth Deemed University Medical College & Hospital and King George Hospital.

Local and systemic adverse reactions at 30 minutes and at 0-6 days after the vaccination were monitored to observe if there was pain, swelling, redness at the injection site and fatigue, headache, gastrointestinal symptoms, myalgia and fever as systemic reactions.

The venous blood samples before and 42-47 days after immunization were collected. The antibody level against varicella-zoster virus (VZV) was determined with Fluorescent Antibody to Membrane Antigen (FAMA) method. A greater than fourfold rise in antibody titer compared to baseline was considered seroconversion.

There were no reactions related to vaccine within 30 min after vaccination in either group. The adverse reactions observed from 0-6 days are summarized in the table below:

Group	No. of Subjects	Redness n (%)	Pain n (%)	Fever n (%)	Total n (%)
Test Group	52	0	2 (3.85)	1 (1.92)	3 (5.77)
Control Group	52	1 (1.92)	6 (11.54)	1 (1.92)	7 (13.46)

The immune responses after vaccination are summarized in the table below:

Group	No. of Subjects	Pre-vaccination GMT	Post-vaccination GMT	Seroconversion rate (%)
Test Group	52	1:9.39	1:58.30	92.31
Control Group	52	1:9.77	1:52.40	80.77

This phase III clinical trial in India showed that seroconversion rate and GMT in test group after immunization were higher at 92.31% and 58.30 respectively although not statistically significant.

Local adverse reactions after test vaccine were mild and there were no severe local and systemic adverse reactions or vaccine-related diseases.

It was concluded that Changchun BCHT's product had good safety and immunogenicity as compared to Varilrix.

Gelatin – Role in Anaphylactic Reaction to Vaccines

It is necessary to maintain the immunogenicity of attenuated vaccine virus during production and storage of vaccines containing live attenuated viruses. Certain additives like stabilizers are added to vaccine formulations primarily to improve vaccine stability upon storage. Stabilizers inhibit chemical reactions, keep the vaccine homogenous and prevent components separating or sticking to the vial during transport and storage.

Gelatin, which is partially hydrolyzed collagen, usually of bovine (cow) or porcine (pig) origin, has been used as stabilizer in many vaccines, including varicella vaccine, as a stabilizer.[1]

The gelling characteristics of gelatin prevent inactivation of the virus from environmental changes such as temperature.[2]

However, there have been concerns with the animal-sourced gelatin coming from cow or pig that it may carry potential animal virus, causing human cavernous encephalitis and other infectious diseases.[3]

More importantly, immediate and/or anaphylactic reactions to vaccines such as measles vaccine or combination measles, mumps, and rubella (MMR) vaccine had been reported in 1980s.[4] Subsequently, similar anaphylactic reactions were reported following vaccination with other vaccines such as varicella vaccine,[5] Japanese encephalitis vaccine[6] and rabies vaccine.[7]

Serological tests have shown that antibodies to gelatin were responsible for these anaphylactic reactions. 80% of children who had immediate-type of allergic reactions were found to have anti-gelatin IgE. A strong relationship was found between immediate type of allergic reactions to JE vaccine and the presence of specific IgE to gelatin. A similar relationship was also found between immediate type of allergic reactions to live virus vaccines (e.g., measles, rubella, mumps, varicella vaccines) containing gelatin and the presence of anti-gelatin IgE in these patients.[6]

It was also reported that children with systemic immediate-type reactions to vaccines showed a booster response of IgE antibody to gelatin. These children were probably sensitized to gelatin present in previous vaccine injections and/or foods.[8]

Removal of gelatin from vaccine formulation dramatically reduced the incidence of anaphylactic reactions as seen in Japan. Data generated by Reporting System for Adverse Events by Ministry of Health and Welfare in Japan from October 1994 - March 2002 showed that the incidence of adverse events per 10,000 doses of live measles vaccine was the highest during October 1995 and March 1996, i.e., 1.79 per 10,000 doses when the live measles vaccine contained gelatin. The rate has decreased steadily as more and more manufacturers removed gelatin from the vaccine formulation

and from April 2001 to March 2002 the rate was the lowest, i.e., 0.22 per 10,000 doses, a reduction of 88%. There were no reports of anaphylaxis by the Monitoring System as of April 2003.[9,10]

The safety of gelatin free NEXIPOX® formulation has been evaluated in China by Yun-hua B et al [3] and Yan T et al.[11] In both the studies it elicited excellent immunogenicity and was well tolerated.

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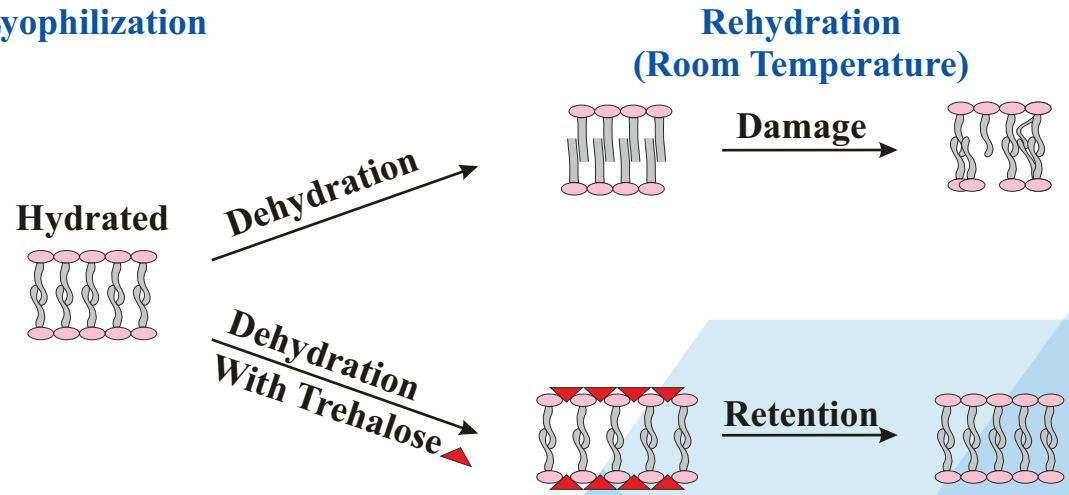
Trehalose In Vaccines

Acquired thermotolerance (including that for a live attenuated lyophilized vaccine) is due to 2 different independent mechanisms, one to induce protection from and second to induce repair of heat stress/ damage on storage. The heat shock proteins (hsps) appear to be required for repair of heat-induced damage. These repair functions are important primarily for recovery after severe heat stress during which damages to macromolecules have accumulated, with lethal consequences in the absence of repair. On the other hand, hsps-independent mechanisms like the accumulation of trehalose may be important for protection during the severe heat stress, preventing the occurrence of damages.[1]

Trehalose is considered to have an important role in survival of organisms, stabilizing membranes and proteins in the face of stress.[2] When baker's yeast is submitted to a heat shock, it accumulates high concentrations of trehalose – up to 35% of the dry weight, conferring yeast the ability to survive desiccation.[3,4]

The major disadvantage of a live attenuated vaccine is the maintenance of 'cold-chain', a costly affair. Therefore, it is desirable for an ideal stabilizer to maintain recommended titer in a vaccine for an extended period at a given temperature. It is known that the trehalose protects cell membrane, protein and other molecules from drying and also preserves the natural biological activity of the molecules. It forms a protective layer around the protein and other biomolecules protecting biological/s under adverse conditions like extreme temperatures, hypertonia and dehydration.[5]

In a desiccating environment, trehalose dries as a transparent glass and results in vitrification. This prevents the expansion of fluids and cells from disruption. Trehalose provides a micro scaffold and supports the tertiary structural integrity of biomolecules and reduces degrading molecular reactions to insignificant levels. It is inert, non-toxic, non-hygroscopic and re-dissolves exhibiting solubility.[5]



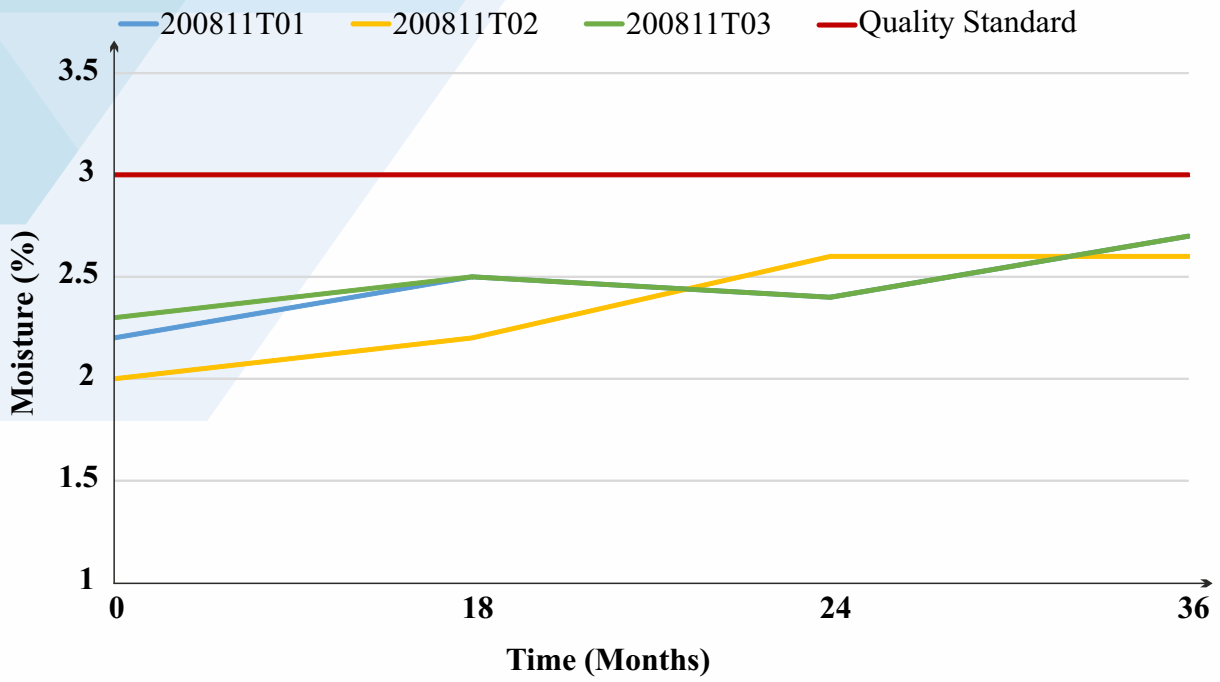
In cases of desiccation, the disaccharide enables organisms to survive even when 99% of their water content has been removed. Water replacement theory states that this is achieved by the replacement of water with trehalose in the organism through hydrogen bonding interactions with polar groups on membrane lipids and proteins. It has also been hypothesised that trehalose modifies the tetrahedral hydrogen-bond structure of water, rearranging the remaining water molecules around biological structures. The amount of water at the interfaces of biomacromolecules and membranes is reduced, and structural modifications to cellular organelles that would cause damage can hence be avoided [6].

Vaccines, particularly live attenuated ones, are either frozen or stored under refrigeration. Further, various vaccine products are processed by lyophilization to enhance their storage stability. Trehalose was reported to be successful in providing protection against dehydration occurring with freeze drying. The storage stability of the lyophilized influenza virus was significantly improved in comparison with its liquid form; retention of 100% hemagglutinin (HA) titer in comparison with less than 20% following 12 weeks of storage at 25°C for lyophilized and liquid influenza virus, respectively.[7]

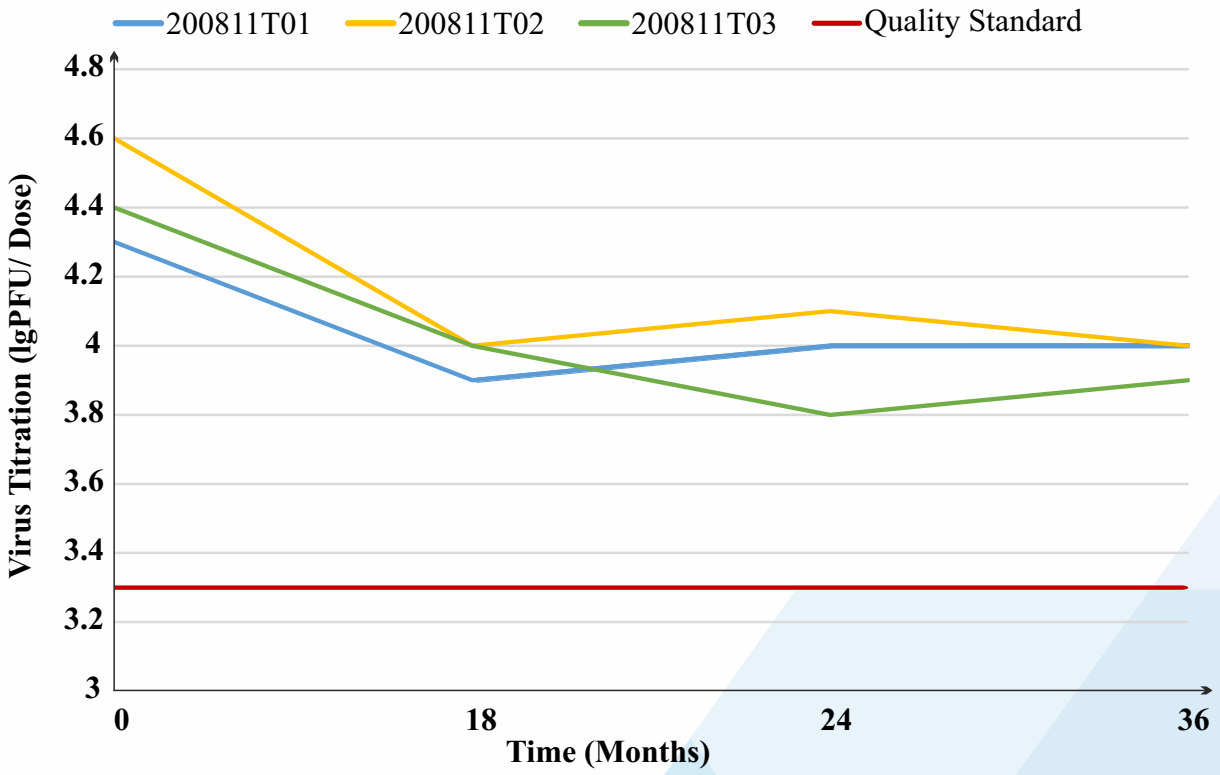
Trehalose has been reported to preserve immunogenicity of even freeze-dried, whole inactivated avian influenza H5N1 virus vaccine by stabilizing the viral particle structure and protecting the viral ssRNA from degradation. It has been reported that no substantial loss of immunogenicity was observed after storage of freeze-dried whole inactivated virus for 3 months at 40°C. Trehalose is shown to have the capacity to stabilize lipid bilayers. The mode of action of trehalose is presumably by replacement of the water molecules situated in between the hydrophilic heads of the lipids. Thereby, a detrimental phase transition of the viral membrane upon rehydration is prevented and the vaccine particles are preserved.[8,9]

NEXIPOX® is gelatin free and contains trehalose as a stabilizer. In-house accelerated stability testing was conducted at 37°C for a month as also real time stability at 2-8°C for 3 years. The main parameters studied for favorable effect by trehalose were moisture content and virus titration. Increasing values of moisture content are seen over time, as was expected but was noted to be within the quality parameters. The virus titration showed a reducing trend, however, the rate of regression of virus titration was seen to be minimal and much above the permissible as per quality standards, making NEXIPOX® highly stable and the only varicella vaccine with a 3 years shelf life while maintaining a PFU of $\geq$ 3.3 lg PFU even on the last day of expiry.

Moisture Trend In Real - Time Stability Test



Virus Titration Trend In Real - Time Stability Test



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Varicella Vaccine - Special Concerns

Breakthrough Varicella

Varicella occurring in vaccinated people more than 42 days after vaccination also referred to as "breakthrough varicella" is always due to wild-type varicella zoster virus (VZV). The clinical presentation is highly modified in the majority of patients as approximately 70% have mild or no fever and most have atypical rash with <50 lesions that are predominantly maculopapular and rarely vesicular.[1] Breakthrough varicella is generally milder (e.g. involves fewer lesions, mostly papules, a lower rate of fever and shorter duration) than natural varicella. In one study, it was observed that time from varicella vaccination was the most important risk factor for varicella breakthrough with most of the failures occurring in the 5-6 years age group.[2]

Lesions in breakthrough varicella cases may be so few in number that they escape observation and present challenges for confirming the diagnosis. Recipients of 2 doses of varicella vaccine are less likely to have breakthrough varicella than those who received one dose by 2-3 folds.[3]

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Varicella Vaccination in Adolescents and Adults

In tropical climates, the majority of studies have described later acquisition of varicella with a significant proportion of cases occurring in adults which are more severe. A progressive increase in seroprevalence with age has been reported in India. 16% of children aged 1-4 years, 54% of children aged 5-14 years and 72% of those aged 15-25 years are found to be infected.[1] This points to a higher overall mean age of varicella infection compared with temperate climates and associated higher morbidity.

With the decline in disease incidence in the age group 1-4 years, the opportunity for exposure at younger ages has decreased. Therefore, susceptible or partially protected children who reach an older age, when exposed to varicella virus can result in more severe disease. The targeting of varicella vaccination efforts toward older age groups was considered a priority.[3]

Vaccination of susceptible adolescents from age 12 years and beyond can - prevent the higher morbidity and mortality of varicella in older age groups, create a cohort of individuals less likely to develop herpes zoster later in life, mitigate the theoretical increase in herpes zoster with varicella universal routine vaccination (URV) and minimize the risk of a potential upward age-shift of the peak incidence of the disease. It could also reduce the risk of congenital varicella syndrome and neonatal varicella by protecting women of childbearing age.[4]

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One Dose or Two-Dose Schedule

Concerns that cases and varicella outbreaks, although less in number smaller in size, and of shorter duration, might continue to occur in highly vaccinated one dose populations have been raised.[1] This has resulted in adoption of a routine 2 dose policy for children in the United States since 2006: 2-dose vaccination schedule for all children 4-6 years of age and catch-up second dose vaccination for older children, adolescents and adults who had received only 1 dose.[2]

During the first 5 years after introduction of the 2 dose program, the reported varicella incidence was the lowest since the start of the vaccine program (with decline approximately 70% during the 2 dose program), with fewer outbreaks and milder disease.[3]

The Indian Academy of Paediatrics also showed a shift from a one dose schedule to two dose schedule in 2009.[4,5]

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Transmission of Vaccine Virus

Accumulated data from prelicensure studies and postmarketing surveillance suggest that transmission of vaccine strain VZV from healthy persons to susceptible contacts is very rare. In the post-licensure period with >130 million doses distributed, transmission of vaccine strain virus from healthy vaccine recipients to susceptible contacts has been documented by PCR analysis in 11 instances from 9 vaccine recipients (2 vaccinated persons transmitted virus to two contacts) most commonly following household exposure but also in institutional and school settings.[1,2,3]

Transmission occurred only when the vaccine recipient had a rash, including 4 cases from herpes. Additionally, in pre-licensure trials of leukemic recipients of varicella vaccine, only those with skin lesions as a side effect of varicella vaccination spread vaccine strain virus to varicella-susceptible close contacts.[3]

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Herpes Zoster After Vaccination

The Oka strain, like wild-type VZV, may cause latent infection and can reactivate from latency to cause herpes zoster (HZ).

A US study finding of a lower HZ incidence rate among vaccinated children was reportedly consistent with other population-based studies and was the first to demonstrate lower incidence in vaccinated children aged 10 and older. This study provided more evidence that childhood varicella vaccination reduces HZ risk. Further, HZ incidence due to vaccine-strain VZV was seen to be lower than that due to wild-type VZV.[1]

Importantly, studies have documented that both immunocompetent and immunocompromised children vaccinated with varicella vaccines are at reduced risk for vaccine strain VZV HZ as compared with the risk for HZ from wild-type VZV in children with a history of varicella. Among immunocompromised children, one study indicated that varicella vaccine was 100% effective in preventing HZ among HIV-infected children[2] and a pre-licensure study found the risk for HZ was approximately 65% less among leukemic children who had received the varicella vaccine compared with those with previous wild-type varicella infection.[3]

In population-based studies of healthy vaccine recipients, a 4 to 12 times lower risk of HZ among vaccinated children aged <10 years has been reported compared to children with a history of varicella and Weinmann et al found that among children age <18 years HZ incidence was 79% lower among vaccinated than among unvaccinated and that wild-type virus caused half of HZ cases among vaccinated children.[4]

During the whole observation period of NEXIPOX® in a clinical trial conducted at Guang Xi, in 2006, no case of Chickenpox caused by horizontal transmission of vaccine virus strain appeared.

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Prescribing Information

NEXIPOX®

Drug Name

Generic name: Varicella Vaccine (live) I.P. freeze dried

Specification

After reconstitution, each 0.5ml vial/dose of Varicella vaccine OKA strain ≥ 2000 PFU

Characters and Constituents

A lyophilized preparation (with appropriate stabilizer) of the live attenuated varicella-zoster virus (OKA strain) obtained by propagation of the virus in human diploid cell culture. This product is a milky white crisp cake in the glass vial. The reconstituted vaccine after dissolution with sterile diluent is a clear solution.

Composition

A lyophilized vial containing

Varicella zoster virus, Live vaccine OKA strain	≥2000 PFU
Mannitol	5mg
Dextran	12.5mg
Sucrose	25mg
Trehalose	10mg
Human Albumin	5mg

A vial with 0.5ml Sterile Water for Injection I.P.

Function and Use

After vaccination, the body's immune-activity against varicella can be generated for preventing the person from acquiring varicella infection.

Administration and Dosage

1. Reconstitute the vaccine with the stated amount (0.5ml) of Sterile Water for Injection and shake well to ensure complete dissolution of the milky white crisp cake before use.

2. Inject 0.5ml of the reconstituted vaccine, subcutaneously at the deltoid insertion area of the lateral aspect of the upper arm.

3. Alcohol and other disinfectant can inactive the attenuated virus in the vaccine, therefore, the

vaccine should be injected immediately after the disinfectant is evaporated completely from the skin.

Contact with disinfectant must be avoided.

4. NEXIPOX® should not be administered intra-dermally (ID) or intra-venously (IV). It is recommended to use the vaccine as soon as it is reconstituted.

DISCARD RECONSTITUTED VACCINE IF NOT USED WITHIN 30 MINUTES.

Indication

The vaccine is indicated for the active immunization against varicella of healthy varicella susceptible subjects from age of 12 months.

Dosage

Children: 2 doses of Varicella vaccine should be given from 12 months to 12 years of age, at least 3 months apart in healthy subject.

Adolescents & Adults: 2 doses of Varicella vaccine should be given for primary immunization in healthy subject, 4 to 8 weeks apart.

Undesirable Effects / Side Effects

Very low overall reactogenicity in all the age groups studied. Reactions at the site of injection are usually mild and temporary. In a clinical trial involving 600 children, it was observed that papulovesicular eruptions appeared in less than 4% of all vaccines and fever (axillary temperature over 37.5°C) occurred in less than 5% of cases. There is no statistically significant difference in the trials of this product with the reference vaccine.

Contraindications

The vaccine should not be used under the following conditions:

1. Subjects with known hypersensitivity to any constituent of this product including neomycin.
2. Women during pregnancy.
3. Subject suffering from serious diseases (acute or chronic infection), fever and any advanced immune disease.
4. Subjects treated with steroidal drug.
5. Subjects with a total lymphocyte count of less than 1200 per mm^3 or presenting other signs of cellular immunodeficiency.
6. Subjects with known history of congenital immune disease or having closely touched with the family member who has a history of this disease.

Warnings and Precautions

1. It is advisable to have a solution of epinephrine available in the case of anaphylactic reaction.

2. Generally speaking, it is advisable to keep the subject under medical supervision for 30 minutes following vaccination of this product.

3. Transmission of vaccinal virus only occurs in extremely rare cases. Contact should be avoided with patients who may develop severe varicella, such as patient suffering from leukemia or who are undergoing immune-suppressant therapy, especially when the vaccine develops a cutaneous reaction 2 to 3 weeks after vaccination. All contact with pregnant women who may contract varicella should be avoided, especially in the first 3 months of pregnancy.

4. Administered subcutaneously, not intra-dermally and never, under any circumstances, intravenously.

a. Transfer the diluent in one of the vials with a syringe into the vial containing lyophilized vaccine, shake well to ensure complete dissolution of the milky white crisp cake for use and transfer all the liquid back to the syringe.

b. Inject 0.5ml solution for subcutaneously at the deltoid area of the upper arm.

c. Alcohol and other disinfectant may inactivate the attenuated virus, thus the vaccine should be applied right after ensuring the complete evaporation of the disinfectant away from the skin.

5. Contact of any disinfectant with the vaccine of this product during opening and injecting of the vial and unclear label of glass vial.

6. Do not administer injection in condition of incomplete dissolution of this product, cracked glass vial and unclear label of glass vial.

7. It is recommended to use the vaccine as soon as it is reconstituted with SWFI.

8. Avoid administration of other vaccines within 1 month following vaccination of this product.

9. Patients with leucocythemia, tumor or immunodeficiency should use the vaccine restrainedly under doctor's guidance.

10. Attenuated live vaccine is not recommended to be used during epidemic seasons.

Interaction with Other Medicines

Product must not be used in case of individuals who have been transfused with whole blood, plasma or immunoglobulins within 5 months before vaccination or within 3 weeks after vaccination as efficacy of vaccine is likely to be reduced. Avoid the use of Salicylate within 6 weeks following vaccination of this product. There should be a one month interval between inoculation of other live attenuated vaccines.

Pregnancy and Lactation

Women of child bearing age can be vaccinated only if appropriate contraceptive measure have been taken for at least 3 months following vaccination. It is not known whether the vaccine is excreted in human milk, because many drugs are excreted in human milk. Caution should be paid to women in lactation period.

Effects on Ability to Drive and Use Machines

It is not known whether the vaccine may affect the ability to drive and use machines, caution should be paid.

Antidote for Overdosing

Not Known

Shelf Life

36 months

Shelf Life after Dilution or Reconstitution

It is recommended to use the vaccine as soon as possible when it is opened.

Storage

Vaccine should be stored in refrigerator and transported with cold chain in dark between +2°C to + 8°C.

DO NOT FREEZE

Dosage Form

One vial of Varicella Vaccine (Live) I.P along with One Vial of Sterile Water for Injection (as Diluent)

Nature and Specification of the Container

Kit for injection contains two 2ml glass vials. The milky white crisp cake of lyophilized vaccine is in one vial and the Sterile Water for Injection (diluent) is in another vial.

This injection kit is used for 1 person in a single dose.

Instructions for Use

The vaccine must be administered by a professional health care personnel or doctor.

The vaccine should not be inoculated with the same syringe for other vaccine.

The vaccine must under no circumstances to be administered intravenously or intramuscularly.

The vaccine is to be administered by subcutaneous injection only.

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