Changchun BCHT Biotechnology Co.

Add: 1260 Huoju Road, Changchun High-tech Zone, Changchun, Jilin 130012, P.R. China
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Url: http://www.bchtpharm.com

Annexure C to Module I

1. Name of the medicinal product

Chikvax® 3.3lg PFU/0.5ml, powder and solvent for solution for injection.

2. Qualitative and quantitative composition

One dose (0.5 ml) contains:
Live attenuated varicella-zoster (Oka strain) virus* 3.3lg plaque forming units (PFU)
*propagated in MRC5 human diploid cells

For excipients, see 6.1.

3. Pharmaceutical form

Powder and solvent for solution for injection. Clear peach to pink coloured solution.

4. Clinical particulars

4.1 Therapeutic indications

Chikvax is indicated for active immunisation against varicella in healthy adults and adolescents (= 13 years) who have been found to be seronegative with respect to the varicella-zoster virus and are, therefore, at risk of developing chickenpox.

Chikvax is not indicated for routine use in children. However, it may be administered to seronegative healthy children of 1-12 years of age who are close contacts (e.g. household) of persons considered to be at high risk of severe varicella infections.

4.2 Posology and method of administration

Posology

Children 1-12 years, adolescents (= 13 years) and adults

Two doses (each of 0.5 ml of reconstituted vaccine) should be given, with an interval between doses of at least 6 weeks but in no circumstances less than 4 weeks.

One dose of Chikvax may be administered after a first dose of another varicella containing vaccine (see section 5.1).

There are insufficient data to determine the long-term protective efficacy of the vaccine. However, there is currently no evidence that further doses are routinely required following completion of a two-dose regimen in healthy adolescents and adults (see section 5.1).

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If Chikvax is to be administered to seronegative subjects before a period of planned or possible future immunosuppression (such as those awaiting organ transplantation and those in remission from malignant disease), the timing of the vaccinations should take into account the delay after the second dose before maximal protection might be expected (see also sections 4.3, 4.4 and 5.1). Chikvax should not be administered to children aged less than one year.

Elderly
There are no data on immune responses to Chikvax in the elderly.

Method of administration

Chikvax is for subcutaneous administration only. The upper arm (deltoid region) is the preferred site of injection.

Chikvax should not be administered intradermally.

Chikvax must under no circumstances be administered intravascularly.

Chikvax must not be mixed with any other medicinal product in the same syringe (see also sections 4.5 and 6.2).

4.3 Contraindications
Chikvax is contra-indicated in subjects who have a history of hypersensitivity to neomycin, or to any of the excipients in the vaccine, or to any other varicella vaccine.

A second dose of Chikvax is contra-indicated in subjects who have had a hypersensitivity reaction following the first dose.

Chikvax is contra-indicated during pregnancy and breast-feeding (see also sections 4.4 and 4.6).

Furthermore, pregnancy should be avoided for 1 month following vaccination (see section 4.6).

Chikvax must not be administered to subjects with primary or acquired immunodeficiency states with a total lymphocyte count less than 1,200 per mm^3 or presenting other evidence of lack of cellular immune competence, such as subjects with leukaemias, lymphomas, blood dyscrasias, clinically manifest HIV infection, or patients receiving immunosuppressive therapy (including high dose corticosteroids).

Severe humoral or cellular (primary or acquired) immunodeficiency, e.g. severe combined immunodeficiency, agammaglobulinemia and AIDS or symptomatic HIV infection or an age-specific CD4+ T-lymphocyte percentage in children below 12 months: CD4+ <25%; children

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between 12-35 months: CD4+ < 20%; children between 36-59 months: CD4+ < 15% (see section 4.4).

Administration of Chikvax must be postponed in subjects suffering from acute, severe febrile illness. In healthy subjects the presence of a minor infection, however, is not a contraindication.

4.4 Special warnings and precautions for use

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic reaction following the administration of the vaccine.

Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

Serological studies of efficacy and post-marketing experience indicate that the vaccine does not completely protect all individuals from naturally-acquired varicella and cannot be expected to provide maximal protection against infection with varicella-zoster virus until about six weeks after the second dose (see section 5.1).

Administration of Chikvax to subjects who are in the incubation period of the infection cannot be expected to protect against clinically manifest varicella or to modify the course of the disease.

The rash produced during naturally-acquired primary infection with varicella-zoster may be more severe in those with existing severe skin damage, including severe eczematous conditions. It is not known if there is an increased risk of vaccine-associated skin lesions in such persons, but this possibility should be taken into consideration before vaccination.

Transmission of the vaccine viral strain

Transmission of vaccine viral strain has been shown to occur from healthy vaccinees to healthy contacts, to pregnant contacts and to immunosuppressed contacts. However, transmission to any of these groups occurs rarely or very rarely and has not been confirmed to occur in the absence of vaccine-associated cutaneous lesions in the vaccinee (see section 4.8).

In healthy contacts of vaccinees, seroconversion has sometimes occurred in the absence of any clinical manifestations of infection. Clinically apparent infections due to transmission of the vaccine viral strain have been associated with few skin lesions and minimal systemic upset.

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However, contact with the following groups must be avoided if the vaccinee develops a cutaneous rash thought likely to be vaccine-related (especially vesicular or papulovesicular) within four to six weeks of the first or second dose and until this rash has completely disappeared (see also sections 4.6 and 5.1).

- varicella-susceptible pregnant women and

- individuals at high risk of severe varicella, such as those with primary and acquired immunodeficiency states. These include individuals with leukaemias, lymphomas, blood dyscrasias, clinically manifest HIV infections, and patients who are receiving immunosuppressive therapy, including high dose corticosteroids.

In the absence of a rash in the vaccinee, the risk of transmission of the vaccine viral strain to contacts in the above groups appears to be extremely small. Nevertheless, vaccinees (*e.g.* healthcare workers) who are very likely to come into contact with persons in the above groups should preferably avoid any such contact during the period between vaccinations and for 4-6 weeks after the second dose. If this is not feasible, then vaccinees should be vigilant regarding the reporting of any skin rash during this period, and should take steps as above if a rash is discovered.

Healthy seronegative children may be vaccinated if they are close contacts of persons who are at high risk of severe varicella infection (see sections 4.1 and 4.2). In these circumstances, continued contact between the vaccinee and the person at risk may be unavoidable. Therefore, the risk of transmission of the attenuated vaccine viral strain from the vaccinee should be weighed against the potential for acquisition of wild-type varicella-zoster by the at-risk person.

The Oka vaccine viral strain has recently been shown to be sensitive to acyclovir. Vaccination may be considered in patients with selected immune deficiencies where the benefits outweigh the risks (e.g. asymptomatic HIV subjects, IgG subclass deficiencies, congenital neutropenia,chronic granulomatous disease, and complement deficiency diseases).

Immunocompromised patients who have no contraindication for this vaccination (see section 4.3) may not respond as well as immunocompetent subjects, therefore some of these patients may acquire varicella in case of contact, despite appropriate vaccine administration. These patients should be monitored carefully for signs of varicella.

4.5 Interaction with other medicinal products and other forms of interaction

In subjects who have received immune globulins or a blood transfusion, vaccination should be delayed for at least three months because of the likelihood of vaccine failure due to passively acquired antibody to the varicella-zoster virus.

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Aspirin and systemic salicylates should not be given to children under the age of 16, except under medical supervision, because of the risk of Reye's syndrome. Reye's syndrome has been reported in children treated with aspirin during natural varicella infection. However, there is no evidence to suggest that vaccination with Chikvax should be contraindicated for older age-groups who need to take aspirin.

In a study in which Chikvax was administered to toddlers at the same time as, but at a different site to, a combined measles, mumps and rubella vaccine, there was no evidence of significant immune interference between the live viral antigens.

If a measles containing vaccine is not given at the same time as Chikvax, it is recommended that an interval of at least one month between vaccinations is respected, since it is recognised that measles vaccination may cause short-term suppression of the cell-mediated response.

If it is considered necessary to administer another live vaccine at the same time as Chikvax, the vaccines must be given as separate injections and at different body sites.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnant women should not be vaccinated with Chikvax.However, fetal damage has not been documented when varicella vaccines have been given to pregnant women.

Pregnancy should be avoided for 1 month following vaccination. Women who intend to become pregnant should be advised to delay.

Lactation

The infants of seronegative women would not have acquired transplacental antibody to varicella-zoster virus. Therefore, due to the theoretical risk of transmission of the vaccine viral strain from mother to infant, women should not be vaccinated while breastfeeding.

Fertility

No fertility data are available

4.7 Effects on ability to drive and use machines

It would not be expected that vaccination would affect the ability to drive or operate machinery.

4.8 Undesirable effects

Clinical trials in healthy subjects

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Total sample size in Phase III clinical trials should be 600, 400 in test group and 200 in control group, respectively. Subjects aged range 1-12 years old would be assigned to two sub-groups, Infant Sub-group (age 1 to 5) and Child Sub-group (age 6 to 12), and 300 subjects for each sub-group. Every subject should receive single dose of test vaccine or control vaccine randomly. Compliances for immunogenicity and safety observation were 88.00% and 100.00%, respectively, which both met protocol requirements.

Total incidences of local adverse reactions in test group and control group were 5.25% and 6.00%, respectively, for which difference had no statistical significance ($X^2 = 0.1443$, $p = 0.7035$). Except for 1 local (0.25%) Grade 2 reactions in test group recorded, no other reactions were observed higher than Grade 2; therefore, difference between two groups had no statistical significance. Difference of incidences of local reaction between Infant sub-group and Child sub-group in test group had no statistical significance. No serious local adverse reactions were observed.

Frequencies are reported as:

Very common:	=10%
Common:	=1% and <10%
Uncommon:	=0.1% and <1%
Rare:	=0.01% and <0.1%
Very rare:	<0.01%

Blood and lymphatic system disorders
Uncommon: lymphadenopathy

Nervous system disorders
Uncommon: headache, somnolence
Very rare: dizziness

Eye disorders
Rare: conjunctivitis

Respiratory, thoracic and mediastinal disorders
Uncommon: cough, rhinitis

Gastrointestinal disorders
Uncommon: nausea, vomiting
Rare: abdominal pain, diarrhoea

Skin and subcutaneous tissue disorders
Common: rash

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Uncommon: varicella-like rash, pruritus
Rare: urticaria

Musculoskeletal and connective tissue disorders
Uncommon: arthralgia, myalgia

Infections and infestations
Uncommon: upper respiratory tract infection, pharyngitis

General disorders and administration site conditions
Very common: pain, redness and swelling at the injection site*, fever (oral/axillary temperature = 37.5°C or rectal temperature = 38.0°C)*
Uncommon: fever (oral/axillary temperature > 39.0°C or rectal temperature > 39.5°C), fatigue, malaise

Very rare: face oedema

Psychiatric disorders

Uncommon: irritability

* Swelling at the injection site and fever were commonly reported in studies conducted in children = 12 years.

In general, the reactogenicity profile after the second dose was comparable to that after the first dose. However, the rates of injection site reactions (primarily redness and swelling) were higher after the second dose in children aged =12 years.

No differences were seen in the reactogenicity profile between initially seropositive and initially seronegative subjects.

Post-marketing surveillance

Nervous system disorders
Febrile and non-febrile convulsions cerebellar ataxia**

Infections and infestations
Herpes zoster**

Immune system disorders
Hypersensitivity, anaphylactic reactions

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** This reaction reported after vaccination is also a consequence of wild-type varicella infection. There is no indication of an increased risk of its occurrence following vaccination compared with wild-type disease.

Transmission of the vaccine virus from healthy vaccinees to healthy contacts has been shown to occur very rarely.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose
Cases of accidental administration of more than the recommended dose of Chikvax have been reported. Amongst these cases, the following adverse events were reported: lethargy and convulsions. In other cases, no associated adverse events were reported.

5. Pharmacological properties

5.1 Pharmacodynamic properties

The Oka strain virus contained in Chikvax was initially obtained from a child with natural varicella; the virus was then attenuated through sequential passage in tissue culture.

Natural infection induces a cellular and humoral immune response to the varicella-zoster virus, which can be rapidly detected following infection. IgG, IgM and IgA directed against viral proteins usually appear at the same time that a cellular immune response can be demonstrated, making the relative contribution of humoral and cellular immunity to disease progression difficult to ascertain. Vaccination has been shown to induce both humoral and cell-mediated types of immunity.

In clinical trials, the immune response to vaccination was routinely measured using an immunofluorescence assay. Antibody titres of = 1:4 (the detection level of the test) were considered as positive.

Efficacy and effectiveness

To observe the adverse reaction and immunogenicity induced by freeze-dried live attenuated varicella vaccine. **Methods** A total of 460 subjects were immunized with domestic freeze-dried live attenuated varicella vaccine, and general adverse reactions and abnormal reactions were

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followed-up 30 min, 6 h, 24 h, 48 h, 72 h and 4 ~ 10 d after immunization. The abnormal reactions within 30 d were collected through telephone and the report by subjects themselves. The antibody titers against varicell-zoster virus （VZV） of the subjects before and after immunization were determined by FAMA, and the antibody positive rate as well as antibody GMT and its increasing fold were calculated. **Results** No severe local or systemic adverse reactions or abnormal reactions were observed in 460 subjects during the whole clinical trial. The total positive of antibody was 98. 31%. The GMT of antibody after immunization was 147. 38, which increased by 38.18 folds compared with that before immunization. The GMT of antibody in subjects aged 6 ~ 12 years were significantly higher than those aged 1 ~ 5 years. **Conclusion** Domestic freeze-dried live attenuated varicella vaccine showed good safety and immunogenicity.

Varicella is an acute infectious and highly contagious disease especially for children caused by varicella-zoster virus (VZV). Almost all people aged about 20 are easy to be infected. Varicella may be accompanied by severe complications, including pneumonia, encephalitis, acute cerebellar ataxia, Reye syndrome and hepatitis, in particular in immunosuppression patients and old people. Reactivation of latent virus may result in herpes zoster (shingles).

5.2 Pharmacokinetic properties
Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data
There is no other relevant information that has not already been stated above.

6. Pharmaceutical particulars

6.1 List of excipients
5 mg-Mannitol, 12.5 mg-Dextran, 25 mg-Sucrose, 10 mg-Trehalose, 5 mg-Human Albumin, per dose.

6.2 Incompatibilities
Chikvax should not be mixed with other vaccines in the same syringe.

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6.3 Shelf life

3 years.
The vaccine should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should normally not be longer than 1 hour at +2°C to +8°C (in a refrigerator). Do not freeze.

6.4 Special precautions for storage
Store at +2°C to +8°C (in a refrigerator).
The lyophilised vaccine is not affected by freezing.

6.5 Nature and contents of container

Powder for reconstitution
Cream to yellowish or pinkish coloured cake or powder in 3 ml vials (Type I glass) with stopper (bromobutyl rubber) and flip-off cap (aluminium).
Solvent for reconstitution
Water for Injections in 1 ml ampoule (Type I glass) or prefilled syringe.
Packs of one.

PFS Details

Manufactuer of PFS	BD
Type of glass they use for syringe	borosilicate glass
Gage of Needle	25G

6.6 Special precautions for disposal and other handling

Due to minor variations of its pH, the colour of the reconstituted vaccine may vary from peach to pink . The diluent and the reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of physical appearance prior to administration. In the event of either being observed, discard the diluent or the reconstituted vaccine.

Instructions for reconstitution of the vaccine with diluent presented in ampoules

Chikvax must be reconstituted by adding the entire contents of the supplied ampoule of water for injections diluent to the vial containing the powder. After the addition of the diluent to the powder, the mixture should be well shaken until the pellet is completely dissolved in the diluent.
After reconstitution, the vaccine should be used promptly.
A new needle should be used to administer the vaccine.
Withdraw the entire contents of the vial.
Alcohol and other disinfecting agents must be allowed to evaporate from the skin before injection of the vaccine since they may inactivate the virus.

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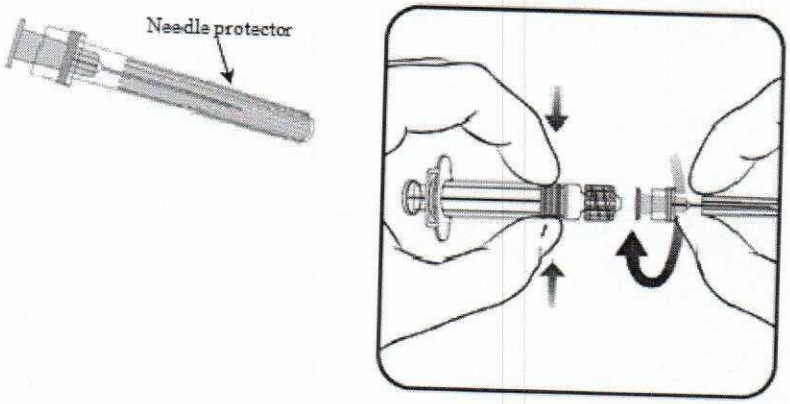
Instructions for reconstitution of the vaccine with diluent presented in pre-filled syringe

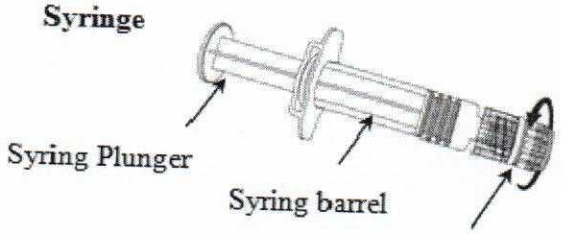
Chikvax must be reconstituted by adding the entire content of the pre-filled syringe of diluent to the vial containing the powder.

To attach the needle to the syringe, refer to the below drawing. However, the syringe provided with Chikvax might be slightly different (without screw head) than the syringe described in the drawing. In that case, the needle should be attached without screwing.

Needle



Syringe



1. Holding the syringe barrel in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.

2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock. (see picture)

3. Remove the needle protector, which on occasion can be a little stiff. Add the diluent to the powder. After the addition of the diluent to the powder, the mixture should be well shaken until the powder is completely dissolved in the diluent.After reconstitution, the vaccine should be used promptly.A new needle should be used to administer the vaccine.Withdraw the entire contents of the vial.

Alcohol and other disinfecting agents must be allowed to evaporate from the skin before injection of the vaccine since they may inactivate the virus.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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7. Marketing authorisation holder

BCHT was established in March 2004 by the investment of Changchun High-technology Industry Development Property (Group). The company is a high-tech enterprise engaged in research, development, production and marketing of biologics and drugs. BCHT now owns four manufacturing sites which cover 235,000 square meters in total and two R&D centers for vaccine and drug with the most equipped laboratories and pilot plants in the areas over 5000 square meters. For the last few years, the company's R&D investment exceeds over 120 million RMB.

Represented by development of the new AIDS preventive vaccine, the company has carried out more than 50 R&D projects in innovative biologics and peptide drugs, resulted in 2 certificates for production and 12 approvals for clinical trial from CFDA. At present, there are 13 key vaccine projects. The company submitted 33 patent applications in which 11 patents have been granted.

BCHT has been awarded as High-tech Enterprise, AAA Credit Enterprise, Quality Creditable Enterprise and assigned as Engineering Research Center for Modern Vaccines, Innovative Center for Science and Technology of Vaccine, Engineering Research Center for Vaccines at Changchun State Bio-Industry Base by Jilin province. BCHT has co-established National Engineering Laboratory for AIDS Vaccine with Jilin University.

In 2008, BCHT successfully launched its product Varicella Vaccine, Live in China. In the following years, BCHT continuously committed to improving the product and led in 2010 removal of gelatin from adjuvant and extended the vaccine shelf-life up to 36 months which is the longest one in the world in 2011. These improvements enhanced the vaccine safety and quality, and established BCHT the leading position in varicella vaccine. At present, the company has 13 key vaccine projects including live attenuated influenza vaccine (LAIV), new rabies vaccine for human use, component acellular DTP vaccine which will be launched to the market in the next few years.

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Jilin Maifeng Biopharmaceutical Co., Ltd., a subsidiary of BCHT, is devoted to mostly R&D in high density cell culture technique and its application for large scale production. Jilin Maifeng is the first company to develop and apply the self-developed microcarrier bioreactor technology to produce rabies vaccine for human use.

BCHT is in a fast-growing stage to approach the advanced international level in quality, marketing, management and human resource, aiming at becoming a first-class biopharmaceutical enterprise in the world.

8. Marketing authorisation number(s)

Vaccine : 2008S00108

9. Date of first authorisation/renewal of the authorisation

04 Feb. 2008

10. Date of revision of the text

18 Sept. 2012

Place: Changchun

Date: 09TH February 2015

Changchun BCHT Biotechnology Co.

Dr. Jinchang WU