Registration No.: 1C 80/43 (N)

Importer / Manufacturer: Sanofi Pasteur Ltd., Thailand/ The Research Foundation for Microbial Diseases of Osaka University (BIKEN), Japan

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICAL PRODUCT: OKAVAX

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
When the vaccine is reconstituted with the 0.7 mL of solvent supplied water for injection, Japanese Pharmacopoeia (J.P.), one dose (0.5 mL) contains the following:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>Attenuated live varicella-zoster virus (Oka strain) not less than 1,000 PFU</td>
</tr>
</tbody>
</table>

Varicella, like measles and mumps, is representative of contagious childhood diseases and of systemic infectious diseases characterized by eruption and fever.

Professor Takahashi and his collaborators at Research Institute for Microbial Diseases Osaka University, initiated the study into varicella vaccine in 1970, which led to the successful development of the first varicella vaccine worldwide.

The initial study of varicella vaccine was performed by "The Study Committee on Varicella Vaccine", supported by the Ministry of Health and Welfare for 3 years from 1973. The varicella vaccine was then further tested clinically over a 3 year period from 1981 by "The Study Committee on Development of Varicella Vaccine" supported by the Ministry of Health and Welfare when its efficacy and safety were proved.

The vaccine is prepared using the attenuated Oka strain of varicella-zoster virus. The seed virus of the Oka strain is incubated and grown in human diploid cells, and the viral suspension is then harvested and purified. Once the stabilizer has been added, the viral suspension is dispensed into vials and lyophilized.

3. PHARMACEUTICAL FORM
   OKAVAX LIVE ATTENUATED VARICELLA VIRUS VACCINE BIKEN™ is a pale white, lyophilized preparation that contains attenuated varicella-zoster virus (Oka strain).

4. CLINICAL PARTICULARS

   4.1 Therapeutic indications
   Prevention of varicella

   PHARMACOLOGY
   Varicella infection occurs via airborne transmission and initially enters through the ocular mucous membranes and/or upper airways, proliferating in local lymph nodes. This results in a primary viraemia and dissemination to systemic organs. After further proliferation in the organs, secondary viraemia ensues, resulting in the clinically apparent disease.
In those having previously received the varicella vaccine, the humoral and cellular immunity established inhibits viral proliferation, thus preventing chickenpox. This immunity is thought to persist for an extended period.

CLINICAL APPLICATION
Clinical studies have established the safety and efficacy of this vaccine in both healthy persons and high risk patients.3, 23 The seroconversion rate among leukaemic children is in the order of 90%, and the protection rate in household contacts is around 80%. The seroconversion rate in other subjects is over 90%. Clinically significant breakthrough cases of varicella in vaccine recipients are less than a few percent. In leukaemia patients undergoing maintenance therapy, it is recommended that immunity against chickenpox be checked 1 to 3 months after vaccination and then monitored periodically thereafter. Should the antibody titre decrease significantly, the vaccine should be re-administered depending on the condition of the patient.

4.2 Posology and method of administration
The vaccine is dissolved with 0.7 mL of solvent (water for injection, J.P.), and usually, one dose of 0.5 mL is injected subcutaneously.

Reference Information
Subjects
This vaccine should be injected to individuals over 12 months of age with no history of varicella who meet the following conditions:

Subjects
High-risk patients in whom varicella may result in serious consequences (i.e. patients with malignant tumors such as acute leukaemia, those with compromised immunity due to treatment, and those who are suspected of compromised immunity).

The following conditions must be met in patients with acute lymphatic leukaemia: (1) Remission has been achieved for not less than 3 months (2) The lymphocyte count is not less than 500/mm³ (3) Positive reactions are seen in the delayed-type skin test using purified protein derivative (PPD) dinitrochlorobenzene (DNCB) or phytohemagglutinin (PHA, 5 mcg/0.1 mL) (4) All drugs other than 6-mercaptopurine as a maintenance chemotherapy are discontinued for not less than 1 week before injection and recommenced not less than 1 week after injection (5) Injection should be avoided during reinforcement therapy for leukaemia or extensive therapy having a strong immunosuppressive effect, such as radiotherapy.

Vaccination of patients with malignant solid tumors should only be performed while tumor growth is inhibited after operation or chemotherapy. The conditions described for leukaemia are also applicable to these patients. Vaccination is not recommended for patients with acute myelogenous leukaemia, T-cell leukaemia or malignant lymphoma because clinical symptoms are likely to occur and because the antibody titer is not expected to increase significantly in patients who generally show secondary immunodeficiency due to the underlying diseases or drug therapy given for the treatment of these diseases.

In subjects receiving treatment with drugs such as ACTH or corticosteroids for nephrosis or severe bronchitis, vaccination should only be carried out once the clinical condition is stable. Delayed-type skin tests should be conducted prior to administration when secondary cellular immunodeficiency is suspected due to drug treatment. Even if the above criteria are not met (except in cases where immunological competence is seriously affected, for example a lymphocyte count of less than 500 mm³), the vaccine may be given in an emergency as in the case of a susceptible leukaemia patient coming into contact with a varicella case and varicella zoster immunoglobulin (ZIG) not being available. Clinical data show that in these circumstances the symptoms due to natural
varicella are significantly more severe and dangerous than any possible adverse reactions of the vaccine. In this case, the vaccine should be administered within 72 hours of contact. Susceptible individuals in close contact with high risk patients who receive the vaccine may also receive this vaccine in order to decrease the risk of varicella infection. These are in particular the parents and siblings as well as those who are engaged in the care of the patients.

Adults susceptible to varicella such as those who are engaged in medical care and medical students, may also receive the vaccine since varicella is generally more severe in adults. The vaccine is also indicated for susceptible women for the prevention of varicella during pregnancy.

The vaccine may also be useful to prevent or stop the spread of chickenpox in closed communities, such as hospital wards or school dormitories.

### 4.3 Contraindication

Vaccination is contraindicated in patients in the following categories:

- Those clearly suffering from fever.
- Those clearly acutely ill.
- Those having experienced a previous anaphylactic reaction to the vaccine or any of its components.
- Those who are pregnant.
- Those who should not be vaccinated for reasons other than the above.

### 4.4 Special warnings and precautions for use

**General**

The vaccine should be used in accordance with the principles defined in the regulations related to vaccines and practical guide to vaccination.

Before vaccination, the general health condition of the vaccine recipient should be evaluated clinically by a physician and their temperature should be taken.

Although the vaccine does not contain gelatin, rarely symptoms of shock or anaphylactoid reaction may appear (e.g. urticaria, dyspnea, lip oedema, or laryngeal oedema) after administration. The vaccine should be observed after vaccination.

Women of childbearing age should be advised to practice appropriate birth control for approximately one month before vaccination, and should avoid becoming pregnant for at least two months after vaccination.

**Cases requiring careful consideration before vaccination**

The decision to vaccinate patients in the following categories should take into careful consideration the general health condition and findings of a physical examination:

- Those clearly having an underlying illness such as cardiovascular, kidney, liver, or hematological disease or developmental abnormalities.
- Those who within two days previous to vaccination, developed fever or symptoms (such as a rash) indicating an allergy.
- Those with a history of seizures.
- Those previously diagnosed with an immunodeficiency.
- Those suffering from a disease accompanied by abnormal immune system function or those receiving immunosuppressive therapy. See "Dosage and Administration."
- Those suspected of being allergic to any component of the vaccine.

**The elderly**

Since the elderly frequently have decreased physiologic function, it is advisable to carefully evaluate the health condition of the individual before vaccination.
PRECAUTIONS FOR USE
1. Sterilize apparatus using dry heat, autoclave, boiling, ethylene oxide gas or gamma-rays generated from cobalt 60 and cool to room temperature before use for vaccination.
2. Disinfect the stopper of the container and the surrounding areas with alcohol before reconstituting the vaccine with the accompanying solvent. Dissolve the vaccine to achieve a homogenous solution and draw up the required quantity for one dose into a syringe. Care should be taken to avoid any bacterial cross contamination. Do not remove the stopper or transfer the solution to another container.
3. The vaccine should normally be injected into the extensor side of the upper arm after disinfection with alcohol.
4. Ensure that the tip of the needle does not enter a blood vessel.
5. Do not re-use the needle or syringe.
6. The vaccinee should be advised to be relaxed on the day and the day after vaccination, and to ensure that the injection site is kept clean. The vaccinee should immediately consult a physician if symptoms such as fever or convulsions occur after vaccination.

4.5 Interaction with other medical products and forms of interaction
Transfusion and administration of gammaglobulin
This vaccine may not be effective in those receiving blood or gammaglobulin preparations because the vaccine virus may be neutralized by varicella zoster virus antibody. Vaccination of such individuals should be delayed for 3 months or more. For those receiving high-dose gammaglobulin therapy, i.e. 200 mg/kg or greater, such as patients with Kawasaki disease or acute immune thrombocytopenic purpura (ITP), vaccination should be delayed for 6 months or more. If gammaglobulin is administered within 14 days of administration, the vaccine may not be effective. Such individuals should be revaccinated 3 months or more after the initial vaccination.
Other live vaccines
Those receiving other live vaccines (oral polio, measles, mumps, rubella, BCG, or yellow fever vaccine), are advised to wait until 4 weeks or more has elapsed before being vaccinated, as the administration of another live viral vaccine could interfere with the varicella vaccine and reduce its efficacy.

4.6 Pregnancy and lactation

4.7 Effects on the ability to drive and use machines

4.8 Undesirable effects
Adverse reactions
Local reactions:
Rarely, local reactions such as redness, swelling, and induration may occur at the injection site.
Systemic reactions:
Fever and rash occasionally appear in healthy children and adults 1-3 weeks after vaccination. These are transient and usually disappear within a few days. In rare cases, anaphylactoid symptoms (urticaria, dyspnea, lip oedema, or laryngeal oedema for example) may appear.
Rarely, other hypersensitivity reactions may occur immediately after vaccination or in the 24 hours following vaccination with the appearance of rash, pruritus, or fever. Idiopathic thrombocytopenic purpura may appear rarely (1/1,000,000). Purpura, epistaxis, and oral
mucosa bleeding usually appear within 3 weeks of vaccination. Vaccinees who develop this reaction must be carefully observed (e.g. blood test) and follow a suitable treatment. Vaccinating high-risk patients may cause papular and/or vesicular rash accompanied by a fever 14-30 days after vaccination. This clinical reaction is usually seen in about 20% of patients with acute lymphocytic leukaemia. Vaccinating high-risk patients may cause herpes zoster later, but its incidence is the same as or lower than the incidence in non-vaccinated individuals infected with natural chickenpox.

4.9 Overdose

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

5.2 Pharmacokinetic properties

5.3 Preclinical safety data

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<table>
<thead>
<tr>
<th>Buffer</th>
<th>Sodium chloride</th>
<th>1.14 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Potassium chloride</td>
<td>0.03 mg</td>
</tr>
<tr>
<td></td>
<td>Potassium Dihydrogenphosphate</td>
<td>0.29 mg</td>
</tr>
<tr>
<td></td>
<td>Disodium Hydrogenphosphate, 12-water</td>
<td>3.14 mg</td>
</tr>
<tr>
<td>Stabilizer</td>
<td>Purified sucrose</td>
<td>25.0 mg</td>
</tr>
<tr>
<td></td>
<td>Sodium L-glutamate</td>
<td>0.36 mg</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Kanamycin sulfate</td>
<td>7µg (potency) or less</td>
</tr>
<tr>
<td></td>
<td>Erythromycin lactobionate</td>
<td>2 µg (potency) or less</td>
</tr>
</tbody>
</table>

The BME medium is used for cell culture

6.2 Incompatibilities

6.3 Shelf life

2 years

6.4 Special precautions for storage

This vaccine should be kept between +2°C and +8°C. Stability is even better if the vaccine is kept at -10°C. Do not freeze the solvent or reconstituted vaccine. Only the lyophilized powder may be frozen. The expiry date is indicated on the package.

6.5 Nature and contents of container

One vial contains one dose. Solvent (water for injection, J.P.): 0.7 mL per vial is provided.
Upon mixing with the accompanying solvent, it rapidly dissolves, resulting in a colorless or yellow-whitish clear solution.

pH: 6.8 - 8.0

The ratio of osmotic pressure (to physiological saline): approximately 1

6.6 Special precautions for disposal and other handling

Caution

1. Contents should be carefully inspected upon reconstitution, and should not be used if precipitates, foreign matter, or other abnormalities are found.
2. The vaccine must be reconstituted immediately before vaccination and used immediately after reconstitution.
3. The vaccine is sensitive to light and is rapidly inactivated. Keep away from direct light before and after reconstitution.

7. MARKETING AUTHORITY HOLDER
Sanofi Pasteur Ltd., Bangkok, Thailand

8. MARKETING AUTHORIZATION NUMBER(S)
1C 80/43 (N)

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
02 November 2000

10. DATE OF REVISION OF THE TEXT
Date of local approval: 16 August 2007

(The above information is based on the currently approved leaflet)