Unit: Technical Assessment Unit

Public assessment report for biological products

(VARIVAX)

Administrative information:

Trade name of the medicinal product:	VARIVAX"is a vaccine indicated for active immunization for the prevention of varicella in individuals 12 months of age and older.
INN (or common name) of the active substance(s):	Oka/Merck Varicella Virus live attenuated 1350 PFU
Manufacturer of the finished product	Merck, Sharp & Dohme LLC, 770 Sumneytown Pike, West Point, PA 19486 - USA.
Marketing Authorization holder	Merck, Sharp & Dohme, LLC, P.O. Box 4, West Point, PA 19486 – USA.
Applied Indication(s):	Active immunization for the prevention of Varicella in individuals 12 months of age & older
Pharmaceutical form(s) and strength(s):	-Powder & solvent for suspension for subcutaneous injection -Each 0.5 ml dose when reconstituted contains: Oka/Merck Varicella Virus live attenuated 1350 PFU
Route of administration	subcutaneous injection
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

VZV	varicella-zoster virus
PFU	plaque-forming units
PGS	phosphate, gelatin, and sucrose
CFs	Cell factors
HVF	Harvested Virus Fluids
EIA	enzyme immunoassay
EMEA	European Agency for the Evaluation of Medicinal Products
BSA	bovine serum albumin

FC	filled container
(USDA)	United States Department of Agriculture
SPGA	sucrose-phosphate-glutamate-albumin
PBS	phosphate buffered saline
AE	Adverse Event
CP	Commercial Product
SAE	Serious Adverse Event
GMT	Geometric Mean Titer
gpELISA	Glycoprotein Enzyme-Linked Immunosorbent Assay
PE34	Passage Extension 34
Postdose	Post-vaccination Dose
mL	Milliliter
HHS	House standard

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1. **General introduction about the product including brief description of the AI, its mode of action and indications.**

VARIVAX™, the refrigerated formulation varicella vaccine, is a sterile lyophilized product prepared by formulating the attenuated Oka/Merck VZV (varicella-zoster virus) strain propagated in MRC-5 cell culture. Each dose, containing 1350 PFU of the live attenuated Varicella Virus, is approximately 0.5 mL after reconstitution and is administered by subcutaneous injection. PGS,and urea are used as stabilizers in VARIVAX.

2. **Quality aspects:**

2.2.1 Introduction

VARIVAX"is a vaccine indicated for active immunization for the prevention of varicella in individuals 12 months of age and older.

2.2.2 Drug Substance (Active ingredient)

- **General information**

Nomenclature:

The generic name for the varicella vaccine containing the live, attenuated Oka\Merck strain of varicella-zoster virus is varicella vaccine live (Oka\Merck).

Structure

Varicella-zoster virus (VZV) is an alpha herpesvirus and is a member of the *Varicellovirus* genus in the *Herpesviridae* family of viruses. The active component of the vaccine is the live, attenuated Oka/Merck strain of VZV.

General Properties

Varicella-zoster virus (VZV) is comprised of an icosahedral nucleocapsid housing the linear double-stranded DNA genome, which is successively enveloped by a protein-containing tegument and a host-derived lipid envelope. Evidence suggests that both humoral and cellular immune responses contribute to the virus clearance and immunity to reinfection.

- **Manufacture, process controls and characterization:**

- **Manufacture**

Merck Sharpe &Dohme LLC (Merck) West Point, Pennsylvania, U.S. site.

- **Control of Materials.**

All raw materials and culture media used in the production of varicella drug substance are controlled and tested to ensure that quality acceptance criteria are met.

Purchased culture media are prepared only by approved vendors. Audits of vendors are conducted to show that all raw materials and container components used in the manufacture of the culture medium or supplements are satisfactorily sourced, stored, and tested prior to use.

- **Controls of Critical Steps and Intermediates.**

Within each manufacturing process step, critical process parameters (CPPs) and critical quality attributes (CQAs) were determined, as well as appropriate limits and acceptance criteria.

- **Process Validation**

The vaccine bulk manufacturing process was revised in 1998 and was prospectively validated. Process validation was divided into three parts that are representative of the three batch processes used in the manufacture of the dispensed bulk.

- **Characterization.**

-Elucidation of Structure and Other Characteristics

Varicella-zoster virus (VZV) is an alpha herpesvirus and is a member of the *Varicellovirus* genus in the *Herpesviridae* family of viruses. Virions are composed of an icosahedral nucleocapsid containing the linear, double-stranded DNA genome that is successively enveloped by a protein-containing tegument and a host-derived lipid envelope.

- **Specification**

Assays are performed at several stages of vaccine bulk processing to confirm absence of extraneous agents, to verify potency and identity, and to provide a measure of quality and process consistency.

- **Analytical Procedures.**

Assays involved in control of drug substance are performed according to approved methods. Details for each analytical procedure are provided.

- **Batch analysis**.

Release testing results are satisfactory

- **Reference Standards or Materials**.

The reference standard used for control of varicella-zoster virus (VZV) potency and identity testing is a VARIVAX^{TM} filled container (FC) lot for which routine release testing has been completed (house standards). It is stored at < -60 °C.

- **Container closure system**

Varicella-zoster virus (VZV) process intermediates (harvested virus fluids and final bulks) are stored in 316L, 317L, or other appropriate stainless steel cans (10 L).

Packaging Description and Specifications are detailed in the MA file.

- **Stability of drug substance**

The results of these stability studies are detailed in the M.A file and support a maximum hold time of up to 6 years at -60 to -80 °C.

2.2.3 Drug product:

- **Manufacturing Process Development**.

Detailed description of Manufacturing Process Development was submitted

- **Container closure system and their compatibility.**

The vaccine is supplied in glass vials closed by rubber stoppers and capped with aluminum seals and plastic caps. Their corresponding USP/Ph. Eur. Monographs are described.

- **Microbiological Attributes**.

The refrigerator-stable varicella virus vaccine is provided in single-dose vials with no preservative. The vaccine is manufactured using a validated aseptic process, and sterility testing is included as part of release testing for every lot. Validation of container closure integrity is carried out.

- **Compatibility.**

Refrigerated formulation varicella virus vaccine is reconstituted just prior to use with sterile diluent. A test for reconstitution time using sterile diluent is included as part of release testing for every lot. In addition, this test was included in the stability protocol for filled containers using consistency lots and clinical stability lots. Stability data to conclusion of the study show no significant change in reconstitution time. All stability data results are provided.

- **Manufacture of the drug product:**

- Description of manufacturing process and process controls along with manufacturers and responsibilities.

Merck Sharp &Dohme LLC 770 Sumneytown Pike P.O. Box 4 West Point, Pennsylvania, U.S. 19486-0004	Manufacturing and release activities for varicella virus vaccine refrigerator-stable are performed at the West Point, PA and Durham, NC sites.
Merck Sharp &Dohme BV Waarderweg 39 -2031 BN Haarlem Netherlands	Packaging operations and final market release activities

A process flow diagram with the formulation, filling, lyophilization, and packaging processes are provided

- **Control of critical steps and intermediates**

All processes have been validated and critical process parameters are provided.

- **Process validation and / or evaluation.**

All critical process parameters and critical quality attributes met the pre-defined specifications identified in the test protocol. All standard product release testing requirements were also satisfied.

- **Product specification:**

-Specifications are provided
-No novel excipients used in varicella virus vaccine.

- **Reference Standards or Materials.**

Varicella vaccine reference material is used in testing of Filled Container samples in the varicella infectivity assay

- **Container closure system.**

-Carton box containing ten single dose (0.5 ml) vials (glass type I) of lyophilized vaccine with gray bromobutyl or gray chlorobutyl flurotec stopper & flip-off aluminum seal with magenta plastic button & aluminum foil shell (Package A) .
-Carton box containing ten vials of clear glass (type I) of diluent with chlorobutyl rubber stopper & sealed with aluminum seal with gray, plastic flip-off cap (Package B).
-The drawings and physical dimensions for the components are described.

- **Stability of the drug product.**

The stability profile of the PGS-urea stabilized vaccine at 2-8 °C is most properly described by the stability data for the consistency lots. Data through 36 months at 2-8 °C are available, as are data through 36 months at 2-8 °C following storage for 12 months at -20 °C.

4.Non –clinical aspect:

The Varivax vaccine, a live attenuated varicella virus formulation, was developed without conventional preclinical animal studies. Safety and efficiency of the product was evidenced in clinical studies.

5.Clinical aspect:

Clinical Efficacy:

The protective efficacy of VARIVAX administered subcutaneously was established by: (1) a placebo-controlled, double-blind clinical trial, (2) comparing varicella rates in vaccinees versus historical controls, and (3) assessing protection from disease following household exposure.

Clinical Data in Children

One-Dose Regimen in Children

Although no placebo-controlled trial was carried out with refrigerator-stable VARIVAX, a placebo-controlled trial was conducted using a prior formulation containing 17,000 PFU per dose. In this trial, a single dose of VARIVAX protected 96 to 100% of children against varicella over a two-year period. The study enrolled healthy individuals 1 to 14 years of age (n=491 vaccine, n=465 placebo). In the first year, 8.5% of placebo recipients contracted varicella, while no vaccine recipient did, for a calculated protection rate of 100% during the first varicella season. In the second year, when only a subset of individuals agreed to remain in the blinded study (n=163 vaccine, n=161 placebo), 96% protective efficacy was calculated for the vaccine group as compared to placebo.

In early clinical trials, a total of 4240 children 1 to 12 years of age received 1000 to 1625 PFU of attenuated virus per dose of VARIVAX and have been followed for up to nine years post single-dose vaccination. In this group there was considerable variation in varicella rates among studies and study sites, and much of the reported data were acquired by passive follow-up. It was observed that 0.3 to 3.8% of vaccinees per year reported varicella (called breakthrough cases). This represents an approximate 83% (95% confidence interval [CI], 82%, 84%) decrease from the age-adjusted expected incidence rates in susceptible subjects over this same period. In those who developed breakthrough varicella postvaccination, the majority experienced mild disease (median of the maximum number of lesions <50). In one study, a total of 47% (27/58) of breakthrough cases had <50 lesions compared with 8% (7/92) in unvaccinated individuals, and 7% (4/58) of breakthrough cases had >300 lesions compared with 50% (46/92) in unvaccinated individuals.

Among a subset of vaccinees who were actively followed in these early trials for up to nine years postvaccination, 179 individuals had household exposure to varicella. There were no reports of breakthrough varicella in 84% (150/179) of exposed children, while 16% (29/179) reported a mild form of varicella (38% [11/29] of the cases with a maximum total number of <50 lesions; no individuals with >300 lesions). This represents an 81% reduction in the expected number of varicella cases utilizing the historical attack rate of 87% following household exposure to varicella in unvaccinated individuals in the calculation of efficacy.

In later clinical trials, a total of 1114 children 1 to 12 years of age received 2900 to 9000 PFU of attenuated virus per dose of VARIVAX and have been actively followed for up to 10 years post single-dose vaccination. It was observed that 0.2% to 2.3% of vaccinees per year reported breakthrough varicella for up to 10 years post single-dose vaccination. This represents an estimated efficacy of 94% (95% CI, 93%, 96%), compared with the age-adjusted expected incidence rates in susceptible subjects over the same period. In those who developed breakthrough varicella postvaccination, the majority experienced mild disease, with the median of the maximum total number of lesions <50. The severity of reported breakthrough varicella, as measured by number of lesions and maximum temperature, appeared not to increase with time since vaccination.

Among a subset of vaccinees who were actively followed in these later trials for up to 10 years postvaccination, 95 individuals were exposed to an unvaccinated individual with wild-type varicella in a household setting. There were no reports of breakthrough varicella in 92% (87/95) of exposed children, while 8% (8/95) reported a mild form of varicella (maximum total number of lesions <50; observed range, 10 to 34). This represents an estimated efficacy of 90% (95% CI, 82%, 96%) based on the historical attack rate of 87% following household exposure to varicella in unvaccinated individuals in the calculation of efficacy.

Two-Dose Regimen in Children

In a clinical trial, a total of 2216 children 12 months to 12 years of age with a negative history of varicella were randomized to receive either 1 dose of VARIVAX (n=1114) or 2 doses of VARIVAX (n=1102) given 3 months apart. Subjects were actively followed for varicella, any varicella-like illness, or herpes zoster and any exposures to varicella or herpes zoster on an annual basis for 10 years after vaccination. Persistence of VZV antibody was measured annually for 9 years. Most cases of varicella reported in recipients of 1 dose or 2 doses of vaccine were mild. The estimated vaccine efficacy for the 10-year observation period was 94% for 1 dose and 98% for 2 doses ($p<0.001$). This translates to a 3.4-fold lower risk of developing varicella >42 days postvaccination during the 10-year observation period in children who received 2 doses than in those who received 1 dose (2.2% vs. 7.5%, respectively).

Clinical Data in Adolescents and Adults

Two-Dose Regimen in Adolescents and Adults

In early clinical trials, a total of 796 adolescents and adults received 905 to 1230 PFU of attenuated virus per dose of VARIVAX and have been followed for up to six years following 2-dose

vaccination. A total of 50 clinical varicella cases were reported >42 days following 2-dose vaccination. Based on passive follow-up, the annual varicella breakthrough event rate ranged from <0.1 to 1.9%. The median of the maximum total number of lesions ranged from 15 to 42 per year.

Although no placebo-controlled trial was carried out in adolescents and adults, the protective efficacy of VARIVAX was determined by evaluation of protection when vaccinees received 2 doses of VARIVAX 4 or 8 weeks apart and were subsequently exposed to varicella in a household setting. Among the subset of vaccinees who were actively followed in these early trials for up to six years, 76 individuals had household exposure to varicella. There were no reports of breakthrough varicella in 83% (63/76) of exposed vaccinees, while 17% (13/76) reported a mild form of varicella. Among 13 vaccinated individuals who developed breakthrough varicella after a household exposure, 62% (8/13) of the cases reported maximum total number of lesions <50, while no individual reported >75 lesions. The attack rate of unvaccinated adults exposed to a single contact in a household has not been previously studied. Utilizing the previously reported historical attack rate of 87% for wild-type varicella following household exposure to varicella among unvaccinated children in the calculation of efficacy, this represents an approximate 80% reduction in the expected number of cases in the household setting.

In later clinical trials, a total of 220 adolescents and adults received 3315 to 9000 PFU of attenuated virus per dose of VARIVAX and have been actively followed for up to six years following 2-dose vaccination. A total of 3 clinical varicella cases were reported >42 days following 2-dose vaccination. Two cases reported <50 lesions and none reported >75. The annual varicella breakthrough event rate ranged from 0 to 1.2%. Among the subset of vaccinees who were actively followed in these later trials for up to five years, 16 individuals were exposed to an unvaccinated individual with wild-type varicella in a household setting. There were no reports of breakthrough varicella among the exposed vaccinees.

There are insufficient data to assess the rate of protective efficacy of VARIVAX against the serious complications of varicella in adults (e.g., encephalitis, hepatitis, pneumonitis) and during pregnancy (congenital varicella syndrome).

Clinical Safety:

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in clinical practice. Vaccine-related adverse reactions reported during clinical trials were assessed by the study investigators to be possibly, probably, or definitely vaccine-related and are summarized below.

In clinical trials, VARIVAX was administered subcutaneously to over 11,000 healthy children, adolescents, and adults.

In a double-blind, placebo-controlled study among 914 healthy children and adolescents who were serologically confirmed to be susceptible to varicella, the only adverse reactions that occurred at

a significantly ($p<0.05$) greater rate in vaccine recipients than in placebo recipients were pain and redness at the injection site.

Children 1 to 12 Years of Age

One-Dose Regimen in Children

In clinical trials involving healthy children monitored for up to 42 days after a single dose of VARIVAX, the frequency of fever, injection-site complaints, or rashes were reported as shown in Table 1:

Table 1: Fever, Local Reactions, and Rashes (%) in Children 1 to 12 Years of Age 0 to 42 Days After Receipt of a Single Dose of VARIVAX

Reaction	N	% Experiencing Reaction	Peak Occurrence During Postvaccination Days
Fever ≥102.0°F (38.9°C) Oral	8824	14.7%	0 to 42
Injection-site complaints (pain/soreness, swelling and/or erythema, rash, pruritus, hematoma, induration, stiffness)	8913	19.3%	0 to 2
Varicella-like rash (injection site)	8913	3.4%	8 to 19
Median number of lesions		2	
Varicella-like rash (generalized)	8913	3.8%	5 to 26
Median number of lesions		5	

In addition, adverse events occurring at a rate of ≥1% are listed in decreasing order of frequency: upper respiratory illness, cough, irritability, fatigue, disturbed sleep, diarrhea, loss of appetite, vomiting, otitis, headache, malaise, abdominal pain, other rash, nausea, chills, lymphadenopathy, myalgia, lower respiratory illness, allergic reactions (including allergic rash, hives), stiff neck, arthralgia, itching.

Pneumonitis has been reported rarely (<1%) in children vaccinated with VARIVAX.

Febrile seizures have occurred at a rate of <0.1% in children vaccinated with VARIVAX.

Clinical safety of refrigerator-stable VARIVAX (n=635) was compared with that of the licensed frozen formulation of VARIVAX (n=323) for 42 days postvaccination in U.S. children 12 to 23 months of age. The safety profiles were comparable for the two different formulations. Pain/tenderness/soreness (24.8 to 28.9%) and erythema (18.4 to 21.0%) were the most commonly reported local reactions. The most common systemic adverse events (reported by ≥10% of subjects in one or more treatment groups, irrespective of causal relationship to vaccination) were: fever ≥102.0°F, oral equivalent (27.0 to 29.2%), upper respiratory infection (26.9 to 29.7%), otitis media (12.0 to 14.1%), cough (11.0 to 15.1%), rhinorrhea (8.7 to 10.6%), and irritability (6.5 to 11.9%). Six subjects reported serious adverse events.

Two-Dose Regimen in Children

Nine hundred eighty-one (981) subjects in a clinical trial received 2 doses of VARIVAX 3 months apart and were actively followed for 42 days after each dose. The 2-dose regimen of varicella vaccine had a safety profile comparable to that of the 1-dose regimen. The overall incidence of injection-site clinical complaints (primarily erythema and swelling) observed in the first 4 days following vaccination was 25.4% Postdose 2

and 21.7% Postdose 1, whereas the overall incidence of systemic clinical complaints in the 42-day follow-up period was lower Postdose 2 (66.3%) than Postdose 1 (85.8%).

Adolescents (13 Years of Age and Older) and Adults

In clinical trials involving healthy adolescents and adults, the majority of whom received two doses of VARIVAX and were monitored for up to 42 days after any dose, the frequencies of fever, injection-site complaints, or rashes are shown in Table 2.

Table 2: Fever, Local Reactions, and Rashes (%) in Adolescents and Adults 0 to 42 Days After Receipt of VARIVAX

Reaction	N	% Post Dose 1	Peak Occurrence in Postvaccination Days	N	% Post Dose 2	Peak Occurrence in Postvaccination Days
Fever ≥100.0°F (37.8°C) Oral	1584	10.2%	14 to 27	956	9.5%	0 to 42
Injection-site complaints (soreness, erythema, swelling, rash, pruritus, pyrexia, hematoma, induration, numbness)	1606	24.4%	0 to 2	955	32.5%	0 to 2
Varicella-like rash (injection site) Median number of lesions	1606	3% 2	6 to 20	955	1% 2	0 to 6
Varicella-like rash (generalized) Median number of lesions	1606	5.5% 5	7 to 21	955	0.9% 5.5	0 to 23

In addition, adverse events reported at a rate of ≥1% are listed in decreasing order of frequency: upper respiratory illness, headache, fatigue, cough, myalgia, disturbed sleep, nausea, malaise, diarrhea, stiff neck, irritability, lymphadenopathy, chills, abdominal pain, loss of appetite, arthralgia, otitis, itching, vomiting, other rashes, lower respiratory illness, allergic reactions (including allergic rash, hives).

In a randomized open-label clinical trial (NCT00432523), conducted in France and Germany, 752 children 12 months through 18 months of age received M-M-R II concomitantly administered with VARIVAX at a separate site, by either the intramuscular (n=374) or subcutaneous (n=378) route. In the overall population, 55.3% were male and the median age was 13.2 months. Local and systemic solicited adverse reactions were recorded by parents or guardians using standardized diary cards. Local solicited reactions were recorded for 4 days after vaccination, and systemic solicited adverse reactions were recorded for 42 days after vaccination. In the event that a participant experienced a rash or a mumps-like illness, parents and/or guardians were instructed to contact the investigator for an examination as soon as possible and no later than 72 hours following onset of symptoms. The nature of any rash was characterized by principal investigator either as measles-like, rubella-like, varicella-like or “other”. Study investigators reviewed the diary card with the participant or participant’s legal guardian 42 days after vaccination to ensure consistency with protocol definitions. Table 3 below presents the frequency of solicited adverse reactions based on the final assessment by the study investigators.

Table 3: Proportion of Participants Reporting Solicited Adverse Reactions Following Vaccination with VARIVAX Concomitantly Administered with M-M-R II, by the Intramuscular or Subcutaneous Route

	Intramuscular N=374 %	Subcutaneous N=376 %

Solicited local reactions at Varivax injection site (Days 0 to 4)*		
Erythema†	8.8	16.8
Mild	8.0	12.8
Moderate	0.5	3.7
Severe	0	0
Missing	0.3	0.3
Pain‡	7.0	8.5
Mild	4.8	7.2
Moderate	2.1	1.3
Severe	0	0
Swelling†	3.2	4.8
Mild	1.6	3.5
Moderate	1.1	0.5
Severe	0	0
Missing	0.5	0.8
Solicited systemic adverse reactions (Days 0 to 42)		
Measles-like rash (Days 0 to 42)§	2.9	2.7
Rubella-like rash (Days 0 to 42)§	2.7	2.7
Varicella-like rash (Days 0 to 42)§	0.5	3.2
Mumps-like illness (Days 0 to 42)	0	0.3
Fever (temperature ≥38.0°C) (Days 0 to 42)¶,#	66.5	66.8
38.0-38.5°C	20.4	22.2
>38.5-39.0°C	17.4	16.6
>39.0-39.5°C	14.2	13.4
>39.5-40.0°C	11.8	11.0
>40.0°C	2.7	3.7

N=total number of participants in the group

* During the post vaccination monitoring period (0-42 days), eight participants experienced a varicella-like injection-site rash at the VARIVAX injection site. All were reported in the subcutaneous group.

† Intensity of injection site reaction: mild or ≤2.5 cm; moderate or >2.5 to ≤5.0 cm; severe or >5.0 cm.

‡ Intensity of pain: mild: awareness of symptom but easily tolerated; moderate: definitely acting like something is wrong; severe: extremely distressed or unable to do usual activities.

§ Testing to distinguish between rash caused by wild-type or vaccine virus was not performed. Reports of measles-, rubella-, and varicella-like rash included 3 reports of measles, 1 report of rubella, and 1 report of varicella, all with onset within 15 days post-vaccination.

¶ The percentage of fever is defined within the population who had valid temperature measurements. One participant in IM group and two participants in SC group did not have temperature measurements and were excluded from the denominator; resulting in N=374 and N=376, respectively.

In the IM Group 92.3% of fevers were documented using the rectal route of measurement and 7.7% of fevers were documented only by the axillary route of measurement. In the SC Group 89.6% of fevers were documented using the rectal route of measurement and 10.4% of fevers were documented only by the axillary route of measurement.

Unsolicited adverse events that occurred within 42 days following vaccination were recorded using diary cards supplemented by medical review. Data on unsolicited adverse events were transcribed into the study database during an on-site visit at day 42. The rates and types of reported adverse events (AEs) across groups were similar and included common clinical events that are often reported in the evaluated populations. Serious adverse events occurred at rates of 0.3% and 1% in the intramuscular and subcutaneous groups, respectively. One moderate intensity case of otitis media occurred in a participant in the subcutaneous group was considered related to the vaccination.

Herpes Zoster

Overall, 9454 healthy children (12 months to 12 years of age) and 1648 adolescents and adults (13 years of age and older) have been vaccinated with VARIVAX in clinical trials. Eight cases of herpes zoster have been reported in children during 42,556 person-years of follow-up in clinical trials, resulting in a calculated incidence of at least 18.8 cases per 100,000 person-years. The completeness of this reporting has not been determined. One case of herpes zoster has been reported in the adolescent and adult age group during 5410 person-years of follow-up in clinical trials, resulting in a calculated incidence of 18.5 cases per 100,000 person-years. All 9 cases were mild and without sequelae. Two cultures (one child and one adult) obtained from vesicles were positive for wild-type VZV as confirmed by restriction endonuclease analysis The long-term effect of VARIVAX on the incidence of herpes zoster, particularly in those vaccinees exposed to wild-type varicella, is unknown at present. The long-term effect of VARIVAX on the incidence of herpes zoster, particularly in those vaccinees exposed to wild-type varicella, is unknown at present.

In children, the reported rate of herpes zoster in vaccine recipients appears not to exceed that previously determined in a population-based study of healthy children who had experienced wild-type varicella. The incidence of herpes zoster in adults who have had wild-type varicella infection is higher than that in children.. The incidence of herpes zoster in adults who have had wild-type varicella infection is higher than that in children.

Overall Conclusion:

Varicella virus vaccine live (Oka/Merck) is indicated for vaccination against varicella in individuals 12 months of age and older.
Varicella virus vaccine live (Oka/Merck) is a live, attenuated virus vaccine (a lyophilized preparation of the Oka/Merck strain of varicella, ≥1350PFU) administered subcutaneously or intramuscularly, depending on the market. Following vaccination, live vaccine viruses replicate to induce an immune response.
Overall, Varicella virus vaccine live (Oka/Merck) maintains a favorable benefit-risk ratio against varicella in individuals 12 months of age as confirmed by the available efficacy and safety data.

5.General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.