PUBLIC ASSESSMENT SUMMARY REPORT

Varicella Vaccine, Live

Sinovac (Dalian) Vaccine Technology Co., Ltd., CHINA

What is Varicella Vaccine, Live?

Varicella Vaccine, Live is the Sinovac (Dalian) Vaccine Technology Co., Ltd., trade name for live, attenuated varicella-herpes zoster virus vaccine (Oka strain). Oka strain was obtained from the American Type Culture Collection (ATCC). The vaccine is prepared in SV-1 cell line.

Varicella Vaccine, Live is a white-loose lyophilized preparation, after reconstitution with diluent (Sterile Water for Injection), it should be a clear, colourless to slight opalescence solution. The Vaccine is accompanied with a clear glass Ampoule of 0.5 mL diluent (Sterile Water for Injection) for reconstitution as a single dose.

The Vaccine single-dose vial presentation consists of the following composition per 0.5mL dose:

Components	Quantity (per 0.5 mL)
Active ingredient	
Live Attenuated Varicella-Herpes Zoster Virus (Virus strain: Oka)	Not less than 3.3 lg PFU
Diluent	
Sterile Water for Injection	0.5 mL
Excipients	
Sucrose, Sodium glutamate, Sodium chloride, Potassium chloride, Disodium hydrogen phosphate, Potassium dihydrogen phosphate	

The Vaccine is presented in a 2 mL glass vial of neutral borosilicate glass, with a pharmaceutical grade rubber stopper made out of Brominated butyl rubber stopper, with a cap made of aluminium-plastics combinations. The vaccine is required reconstitution prior to administration with 0.5 mL of Diluent – Sterile Water for Injection (Sterile WFI).

The vial bears a Vaccine Vial Monitor (VVM) type VVM14 affixed on the cap plastic of flip off seal.

The shelf-life of Varicella Vaccine, Live is 24 months at storage conditions 2 – 8°C.

The WFI is clear, colourless liquid of one single dose presented in glass Ampoule (Low borosilicate glass). The manufacturer of the WFI is Jiangsu Desano Pharmaceuticals Co., Ltd. The shelf-life of the Diluent is 48 months with storage conditions 2 – 8°C (as the diluent packed and accompany with the vaccine).

The manufacture of bulks, formulation and filling occur in the facilities of Sinovac (Dalian) Vaccine Technology Co., Ltd., China.

What is Varicella Vaccine, Live used for?

The Varicella Vaccine, Live is indicated for prevention of varicella in children aged 1 year (12 months) to 12 years of age (before 13th birthday).

How is Varicella Vaccine, Live used?

The Varicella Vaccine, Live is colourless to slight opalescence solution liquid when reconstituted to a suspension. The total volume (approximately 0.5 mL) of reconstituted vaccine is administered as a single dose subcutaneously into the outer aspect of the upper arm (deltoid region), immediately after reconstitution.

What is Varicella Vaccine, Live characteristic?

The Varicella Vaccine, Live must be stored between 2 to 8°C. Under the recommended storage conditions, the vaccine is stable for 24 months from the date of manufacture.

Cold chain volume per dose is 94.392 cc in the secondary carton of single-dose vial presentation accompanying with WFI.

Who is the regulatory authority responsible for its oversight vis a vis WHO?

The Varicella Vaccine, Live is manufactured by Sinovac (Dalian) Vaccine Technology Co., Ltd. and licensed in People's Republic of China. The People's Republic of China is the country of manufacturing.

The National Medical Products Administration (NMPA) is the authority responsible for the continuing oversight of this WHO prequalified vaccine.

How has Varicella Vaccine, Live been studied from the clinical point of view?

Clinical data presented in this application by Sinovac include data from three clinical trials:
-A phase 1 trial VZV1001 entitled "A randomized, blind, controlled clinical trial to evaluate the safety of live attenuated varicella vaccine for healthy adults, adolescents and children", Clinicaltrials.gov: NCT02965404
- A phase 3 efficacy study VZV3001 entitled "A double-blind, randomized, placebo-controlled clinical trial to evaluate the efficacy, safety and immunogenicity of live attenuated varicella vaccine in healthy children in China", Clinicaltrials.gov: NCT02981836
- A phase 3 study VZV3002 entitled "A double-blind, randomized clinical trial to evaluate the lot-to-lot consistency, immunogenicity and safety of live attenuated varicella vaccines for children" Clinicaltrials.gov: NCT03555071.

A total of 4283 individuals received Sinovac's Varicella Vaccine, Live (Vvl), including 4223 children aged 12 months to 12 years (the target population). The three clinical trials included in the clinical development of Vvl vaccine were conducted in the Henan Province, China.

Efficacy evaluation: Active surveillance procedures included a visit by the investigator team every 10 days during the epidemic season or every 15 days during the non-epidemic season to ensure case detection. In addition, parents were trained to identify and to report varicella cases and community physicians were also involved in detecting varicella cases in the study population. Each case was under close medical supervision until recovery. Number of lesions were recorded. The primary efficacy endpoint was the occurrence of laboratory confirmed varicella with onset more than 30 days after vaccination during the entire study duration (6-7 months). Lesion fluid specimen were sent to Henan

province, CDC for VZV virus isolation and identification, and to the National Institute for Food and Drug Control (NIFDC) for PCR-RFLP analysis and review of results of virus isolation and identification.

A total of 52 varicella cases were recorded between day 30 to 180 months after vaccination and were confirmed by the DSMB. Out of this total, 45 cases were confirmed by all three laboratory criteria. Six and 46 confirmed varicella cases were reported in vaccine and placebo group, respectively. Overall efficacy estimates against confirmed varicella was 87.1% (95% CI: 69.7, 94.5%) and was 80.2% (95% CI: 10.6, 95.6%), 88.6% (95% CI: 62.2, 96.6%), and 90.2% (95% CI: 23.4, 98.7%) in the 1~4-year, 5~8-year, and 9~12-year-old group, respectively. Efficacy estimates were similar for each study site. There were 24 cases of moderate varicella, all among placebo recipients and vaccine efficacy against moderate cases was 100.0% (95% CI: 83.53, 100.0%). There were no case of severe varicella. Only mild cases were reported in the Vvl group.

The immunogenicity of Vvl vaccine was evaluated in a subset of 703 children of study VZV3001 and in 1145 children in study VZV 3002. Study VZV 3002 was appropriately designed to assess lot-to-lot consistency of immunogenicity of 3 commercial scale lots and non-inferior immunogenicity of commercial scale lots compared to Vvl pilot scale used in the efficacy trial. Varicella virus antibodies were measured by FAMA assay to measure VZV antibody. Lot to lot consistency was well established and the primary endpoint for non-inferiority of commercial scale lots compared to pilot scale lot was met. Overall seroconversion was achieved by 97% of children in study VZV3001 who received a pilot scale lot , by 96.7% of children receiving commercial scale lots and 92.9% of children receiving the same pilot scale lot in study VZV 3002.

The available information based on an extensive population exposure at the dose to be commercialized allows to conclude that, the profile of adverse events observed during the clinical program was expected: local reactions due to injection and systemic reactions due to immunological processes as evidenced by the high reporting rate of fever. The comparison with matching placebo and active licensed comparator is favourable, i.e. no difference between safety profile of tested products and low reporting rate of SAEs. The only term with a significant number of cases (fever) was reported with a very homogenous rate across the three studies (approximately 14%). It can be concluded that – from the available information - the safety profile of the Human diploid cell SV-1 strain based live attenuated varicella vaccine to be used in clinical practice compares with that of the reference vaccine and is acceptable for such a product.

Other information about evaluation of Varicella Vaccine, Live:

As part of the prequalification process for Varicella Vaccine, Live, the Product Summary File (PSF) Document and the responses provided by the manufacturer to observations made by WHO have been reviewed for quality, safety and efficacy by a team of WHO experts, and found to meet WHO requirements of WHO Technical Report Series TRS 848 Annex 1, Varicella vaccine, 1994 (Requirements for varicella vaccine (live).

The manufacturing facility was audited by a WHO team of experts and found to be in compliance with the WHO GMP requirements (WHO TRS 996, Annex 3 2016; TRS 961, Annexes 2, 3 and 6).

WHO has conducted independent testing of batches of the Varicella Vaccine, Live for critical release parameters in contracted laboratories qualified by WHO for the purpose, and results obtained were in compliance with the quality specifications of the product as specified in the WHO TRS 848 Annex 1, Varicella vaccine, 1994.

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