Unit: Technical Assessment Unit

Public assessment report for biological products

Administrative information:

Trade name of the medicinal product:	Varilirix
INN (or common name) of the active substance(s):	Live attenuated varicella virus (OKA strain) ≥ 2000 PFU
Manufacturer of the finished product	**FIDIA Farmaceutici S.p.a** Via Ponte della Fabbrica,3/A 35031 Abano Terme (Padova), Italy. **Corixa Corporation dba GlaxoSmithKline Vaccines** 325 North Bridge Street Marietta, Pennsylvania 17547 USA.
Marketing Authorization holder	GlaxoSmithKline Biologicals SA, Rue de l'Institut, 89, 1330 Rixensart - Belgium
Applied Indication(s):	For active immunization against varicella of healthy subjects from the age of 12 months onward
Pharmaceutical form(s) and strength(s):	Powder and solvent in PFS
Route of administration	Subcutaneous or IM injection
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

GMT	Geometric Mean Titer
TT	Tetanus Toxoid
Td	Tetanus and Reduced Diphtheria Toxoid
DTP	Diphtheria, Tetanus, and Pertussis Vaccine
U/ml	Units per Milliliter
hr	Hour
min	Minute

p	Probability Value
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
IFA	immunofluorescence assay
HSA	Human serum albumin
PFS	Prefilled syringe
PFU	Plaque-forming unit
Ph. Eur.	European Pharmacopoeia
WHO	World Health Organization

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1. **General introduction about the product including brief description of the AI, its mode of action and indications.**
   Varilirx is a lyophilized preparation of the live attenuated Oka strain of varicella zoster virus, obtained by propagation of the virus in MRC-5 human diploid cell culture.
   Varilirx meets the WHO requirements for biological substances and for varicella vaccines.
   Each dose of the reconstituted vaccine contains not less than $10^{3.3}$plauqe-forming units (PFU) of the attenuated varicella zoster virus.

2. **Quality aspects:**

2.2.1 Introduction

As mentioned in the general introduction

2.2.2 Drug Substance (Active ingredient)

- **General information**

Nomenclature:

- Compendial Name (Eu.Ph.): Varicella vaccine (live) Vaccinum varicella vivum
- World Health Organization Name: Live attenuated varicella vaccine, OKA strain

General Prosperities

The varicella monovalent bulk drug substance is a clarified viral suspension diluted in a stabilizer solution containing sorbitol, lactose, mannitol, amino acids, and inorganic salts (free from intact MRC-5 cells). The bulk is stored at -70°C until further use.

The drug substance, formulated as a monovalent varicella vaccine or combined with other drug substances (e.g. combined measles, mumps, rubella, and varicella (MMRV) vaccine, shows to elicit anti-varicella virus antibodies upon administration to subjects aged from 9 months onwards. These antibodies provide protection against varicella virus.

Manufacture, process controls and characterization:

Manufacturer:

GlaxoSmithKline Biologicals SA, Parc de la Noire Epine, Rue Fleming, 20, 1300 Wavre - Belgium

- **Description of Manufacturing Process and Process Controls**

Varicella virus is obtained after multiplication on MRC-5 human diploid working cell bank The production of varicella bulk vaccine is based on the seed lot system and classical cell culture methods are used.

Due to limited yield, it is not possible to produce adequate amounts of varicella virus bulk directly from the working seed. Therefore, an intermediate viral culture, derived from the working seed, is used as inoculum for the bulk vaccine production.

All the critical operations are performed under class 100/A conditions.

- **Control of Materials**

List of raw materials is provided including function, process step and reference. All materials comply either Eu.Ph., USP or with in-house specification. List of starting materials and their manufacturing methods are summarized. TSE/BSE free certificates are provided. The working cell cultures are complying with in-house specifications.

Moreover, MCB and WCB flowcharts are attached. Batch numbering system of MCB and WCB is provided including naming of MCB and WCB of each strain. Specifications of WCB are provided including test method and acceptance criteria. Characteristics of MCB are described.

- **Controls of Critical Steps and Intermediates**

Critical steps that affect the product quality are culture, recovery, clarification and storage. Control parameters of each critical step are listed in a table include the process name, step, IPC and acceptance criteria. Analytical methods are provided.

- **Process Validation**

-The DS manufacturing process has been validated adequately. All process parameters were maintained and all CQA were achieved.

- Tests results of critical quality attribute and results for critical parameter attribute in each stage of DS manufacturing had been demonstrated, aligned with the pre-determined acceptance criteria and show production process consistency.

- **Control of Drug substance:**
  - **Specification**

Table of specifications provided in a tabular form including tests, acceptance criteria and method reference.

  - **Analytical Procedures.**

All analytical procedures either pharmacopeia or in house developed were described. The analytical procedures that need validation are clearly mentioned and well described.

  - **Reference Standards or Materials.**

All reference standards used during manufacturing are well described in the MA file

  - **Container closure system**

Bulks can be stored in three different containers: 1000 mL HDPE bottle with PP cap, 1000 mL HPDE bottle with HDPE cap and PVC gasket and 5 L HDPE container with rubber stopper

- **Stability of drug substance**

- The results of stability studies for three production batches of each DS component support the claimed shelf-life when stored in its proper container.

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**

The varicella vaccine (live) is a freeze-dried preparation presented as a monodose in 3 ml glass vial to be reconstituted with Water for Injection (WFI) diluent. The diluent is presented as 0.5 ml monodose in glass syringe.
The vaccine is reconstituted by adding the entire content of the supplied container of diluent to the vial containing powder. The reconstituted vaccine is a clear peach to pink colored liquid, free from visible particles.

- Container closure system and their compatibility.

The vaccine is presented as a freeze-dried preparation in 3 ml clear glass vial (Type 1, Ph. Eur.). Vials are fitted with bromobutyl rubber stoppers suitable for lyophilisation, aluminium over caps and flip-off caps.
The product is accompanied with diluent WFI in PFS syringe.

- **Manufacture of the drug product:**

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

- **FIDIA Farmaceutici S.p.a** Via Ponte della Fabbrica,3/A 35031 Abano Terme (Padova), Italy is responsible for Formulation, Filling and lyophilization.
- **Corixa Corporation dba GlaxoSmithKline Vaccines**
  325 North Bridge Street Marietta, Pennsylvania 17547 USA is responsible Formulation of varicella vaccine, Filling, lyophilization and Testing of the final bulk.
- **Description of Manufacturing Process and Process Controls**

A flow diagram for the manufacturing process is presented. Critical process parameters and critical quality attributes are indicated on the diagram. Detailed description of the manufacturing process is provided as following: final formulated bulk, filling and sealing then inspection and QC testing. Then finally labeling and packaging.

- **Control of critical steps and intermediates**

There are no intermediate in the DP manufacturing process.
The critical steps of the DP manufacturing process along with the associated in-process tests and acceptance criteria are listed in the dossier.

- **Process validation and / or evaluation**

Process validation is conducted through the whole manufacturing stages. Three consecutive lots manufactured were used. Test results are within the acceptable criterion. The results are summarized. It is verified that the designed production process could produce the product with consistent quality.

- **Control of excipients**

- excipients and their use during the DP manufacturing are mentioned.
- some excipients are compendial and other are non compendial. Analytical procedures are provided. In addition, validation of analytical procedures of non-compendial test are provided.
- these is no excipient from human origin used.

- **Control of drug product**

-The specifications include physical characters, general tests, tests for identity, tests for purity, activity, quantity, tests for contaminants.
- Justification of the DP specifications at the release and during stability studies are provided.
- the analytical procedures, principles and validity criteria used for control testing of the vaccine were provided.

- **Container closure system.**

- The formulation is filled and lyophilized in 3 ml vial containers, sealed with 13 mm ready to sterilize (RTS) stoppers for lyophilized formulations and secured with flip-off caps.
- Identity of materials of construction together with their specifications are described

- **Stability of the drug product.**

-Approved shelf life for the Finished product: 2 years when stored at 2-8°C
-Approved Storage Conditions:
- Store at temperature 2-8ºC. Protect from light.
- the reconstituted vaccine may be kept for up to 90 minutes at room temperature 25ºC. Or up to 8 hours in the refrigerator 2-8ºC

3. Non –clinical aspect:

- Varilrix is a varicella vaccine that is prepared from the attenuated OKA strain. This strain was recommended by the European Pharmacopoeia and WHO for the preparation of varicella vaccines, and its safety and efficacy have been well established. Varilrix vaccine was first registered in Europe in 1994.
- In addition to the well-established efficacy of OKA strain, potency tests for Varilrix are part of the release specifications that are routinely performed on each lot of final container and are submitted as part of the batch analysis results. Varilrix vaccine is clinically immunogenic.
- Secondary pharmacodynamics & Pharmacokinetics studies were not conducted as they are not required for vaccines.
- Good laboratory practice toxicity studies have not been performed with Varilrix vaccine. However, tests for the varicella working seed have been conducted in animals, including: neurovirulence test in

monkeys, extraneous agents test in suckling mice, adult mice and guinea pigs. In addition, general safety tests in mice and guinea pigs have been performed on production lots of the final container vaccine in accordance with the Ph. Eur. and WHO requirements. This was acceptable because the vaccine was first registered in Europe before the EMA's "Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines" came into force. Moreover, Varilrix has been administered to millions of patients in over 90 countries and it was well tolerated and induced appropriate immunological protection in human subjects.

4. Clinical aspect:

➢ Clinical Overview

Varilrix is a live attenuated varicella vaccine (Oka strain) indicated for active immunization against varicella in healthy individuals from 9 months of age. The clinical development program was designed to demonstrate comparability with the currently licensed formulation in terms of immunogenicity, efficacy, safety, and reactogenicity.

The submitted clinical package comprised one pivotal study (OKA-H-186) and three supportive studies (MeMuRu-148, MeMuRu-150, and OKA-H-193) conducted in pediatric populations. The studies evaluated the immunogenicity and safety of the modified formulation (Varilrix mf) following one- or two-dose vaccination schedules and compared the results with those obtained using the licensed Varilrix formulation.

All submitted clinical studies were conducted in accordance with Good Clinical Practice (GCP), as stated by the applicant.

<u>Clinical Efficacy and Clinical Immunogenicity analysis</u>

As protection against varicella is primarily mediated through vaccine-induced immune responses, the clinical efficacy of Varilrix mf was evaluated through established immunogenicity endpoints across four clinical studies involving healthy children receiving one- or two-dose vaccination schedules.

The pivotal study OKA-H-186 demonstrated non-inferiority of Varilrix mf compared with the licensed Varilrix formulation following the first vaccine dose. Comparable anti-varicella-zoster virus (VZV) antibody responses were observed between study groups, with similar geometric mean antibody concentrations/titres measured using both immunofluorescence assay (IFA) and enzyme-linked immunosorbent assay (ELISA). Following administration of the first dose of Varilrix mf, seroconversion rates reached 98.3% as measured by IFA, while ELISA-based seroresponse rates exceeded 90%. After completion of the second dose, all evaluated subjects achieved seroresponse regardless of the assay used.

The supportive studies confirmed these findings. Study MeMuRu-150 demonstrated non-inferiority of Varilrix mf compared with the licensed formulation, with seroconversion rates exceeding 98%, while study MeMuRu-148 reported a seroconversion rate of 97.4% following vaccination with Varilrix mf. In addition, study OKA-H-193 demonstrated comparable anti-VZV antibody concentrations and seroresponse rates between the modified and licensed formulations 42 days after each vaccination dose.

Overall, the clinical data consistently demonstrated robust anti-VZV immune responses, with comparable geometric mean antibody concentrations/titres, seroconversion rates, and seroresponse rates between Varilrix mf and the licensed Varilrix formulation. The submitted evidence supports the conclusion that removal of human serum albumin (HSA) from the vaccine formulation does not adversely affect the immunogenicity or expected clinical effectiveness of Varilrix in the prevention of varicella.

Clinical Safety:

The safety and reactogenicity profiles of Varilrix mf were assessed in the pivotal study and three supportive studies involving a total of 977 children vaccinated during the second year of life.

Across all studies, the incidence, nature, and severity of adverse events were comparable between Varilrix mf and the licensed Varilrix formulation. No new safety concerns were identified following removal of HSA from the formulation.

The most commonly reported adverse events were consistent with the known safety profile of live attenuated varicella vaccines and were generally mild to moderate in intensity and transient in nature.

Importantly, no signals suggestive of an increased incidence of specific adverse events or clinically meaningful differences in adverse event frequencies were observed with Varilrix mf. Study OKA-H-193 further demonstrated non-inferiority of the modified formulation with respect to the occurrence of fever >39.0°C compared with the licensed formulation.

Overall, the safety findings support a comparable safety and reactogenicity profile between Varilrix mf and the currently licensed Varilrix vaccine.

Benefit/ Risk discussion:

Human serum albumin (HSA) was historically included in the Varilrix formulation to support vaccine stability during manufacturing and storage. Subsequent pharmaceutical development demonstrated that removal of HSA did not adversely affect vaccine stability during lyophilization, storage, or reconstitution.

(Varilirix/2000PFU)

Consistent with the objective of minimizing the use of human-derived materials in medicinal products and reducing any theoretical risk of microbial contamination, the applicant developed a modified formulation without HSA.

To ensure that removal of HSA did not affect clinical performance, four clinical studies were conducted comparing the modified formulation (Varilrix mf) with the licensed vaccine. These studies demonstrated comparable immunogenicity, including non-inferiority with respect to seroconversion/seroresponse rates and antibody concentrations. The safety and reactogenicity profiles were also comparable between formulations, with no new or unexpected safety findings identified.

The totality of evidence supports the conclusion that removal of HSA does not adversely impact the efficacy, immunogenicity, or safety profile of Varilrix. Therefore, the overall benefit-risk balance of the modified formulation is considered favorable.

Overall Conclusion:

The submitted clinical data demonstrate that the modified Varilrix formulation without human serum albumin (Varilrix mf) is comparable to the licensed Varilrix formulation in terms of immunogenicity, efficacy, safety, and reactogenicity.

The pivotal and supportive studies consistently demonstrated non-inferior immune responses, high seroconversion and seroresponse rates, and a favorable safety profile without evidence of new safety concerns. Furthermore, the removal of HSA did not adversely affect the clinical performance of the vaccine.

Based on the available clinical evidence, the benefit-risk balance of Varilrix mf is considered positive, supporting its use for active immunization against varicella in the approved pediatric population.

5. General Conclusion and Recommendations if any:

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