Unit: Technical Assessment Unit

Public assessment report for biological products

Eupolio Inj.

Administrative information:

Trade name of the medicinal product:	Eupolio Inj.
INN (or common name) of the active substance(s):	N.A.
Manufacturer of the finished product	LG Chem Ltd. Osong Plant
Marketing Authorization holder	LG Chem Ltd.
Applied Indication(s):	For active primary immunization against poliomyelitis caused by poliovirus in infants from 6 weeks of age.
Pharmaceutical form(s) and strength(s):	Solution for IM injection.
Route of administration	**I.M**
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

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1. **General introduction** Poliomyelitis vaccine is a vaccine to prevent poliomyelitis caused by infection of poliovirus belonging to Enterovirus species. Poliomyelitis generally occurs in children under five years old and in about 0.5 percent of cases, there is muscle weakness resulting in an inability to move. Overall, 5 to 10 percent of patients with paralytic polio die due to the paralysis of muscles used for breathing. As there is no cure for poliomyelitis, it can only be prevented by immunization. As OPV use occasionally has led to the outbreaks of Vaccine-Associated Paralytic Poliomyelitis (VAPP), supply of IPV using Sabin strains is necessary in order to eradicate poliovirus. LG Chem, Ltd. developed the Sabin Inactivated Polio Vaccine through the technology transfer of manufacturing of IPV using Sabin strain from Intravacc. A single human dose (0.5 mL) of Sabin Inactivated Polio Vaccine contains 5 D-antigen units, 8 D-antigen units and 16 D-antigen units of inactivated poliovirus types 1, 2 and 3(Sabin strain), respectively.
2. **Quality aspects:**
   - **2.2.1 As mentioned in the aforementioned section.**
   - **2.2.2 Drug Substance (Active ingredient)**

     It is named inactivated poliovirus types 1, 2, and 3. The poliovirus used in the manufacturing of the drug substance is Sabin strain, and Vero cell line is used for virus cultivation.

The manufacturer is Osong plant of LG Chem, Ltd. is responsible for all manufacturing operations, QC test, stability test, packaging and shipment.

Description of Manufacturing Process and Process Controls.

Vero cells are cultured on micro carrier and infected with working virus seed (WVS) and virus culture is performed. The clarified harvest is concentrated and the highly concentrated virus bulk is purified by size exclusion chromatography (SEC) and anion-exchange chromatography (AEX). Following inactivation, sterile filtration is performed to obtain the inactivated monovalent bulk.

Control of Materials.

List of raw materials of Pharmacopeial and In-House Standard with relevant COAs are provided. Information regarding the used strain & cell substrate is mentioned in detail in the MA file.

Controls of Critical Steps and Intermediates.

Each critical step in the manufacturing process is monitored and controlled in order to assure that inactivated poliovirus types is manufactured under appropriate condition. In-process control (IPC) and quality control test items in the production of inactivated poliovirus types are controlled as quality control.

Process Validation

All critical manufacturing processes were validated by taking three consecutive runs at commercial scale. Process validation batches shall also be subjected to stability studies to evaluate its impact on product quality over the period of time and to justify shelf life of the product. All operating parameters as well as test results met the pre-determined acceptance criteria. All of the results of critical process parameters and non-critical process parameters by each process step showed that the parameters were well-controlled in the established process conditions or operation ranges.

- Manufacturing Process Development.
  - **Characterization.**
    Characterization for inactivated poliovirus was conducted in structural, physicochemical, immunochemical and biological aspects.
    Process-related impurities & Product-related impurities are well illustrated in the MA file & well controlled
  - **Specification**
    Assays involved in control of drug substance are performed according to approved control procedures that describe the main steps in a procedure. The specification for each test is stated in the MA file.
  - **Analytical Procedures.**

Analytical procedures for all test methods employed for in the release and stability tests for drug substance of Sabin Inactivated Polio are well described.

- **Batch analysis.**
  Results of Batch release testing for virus harvest in inactivated poliovirus are mentioned in MA file.
- **Reference Standards or Materials.**
  Results of Batch release testing for virus harvest in inactivated poliovirus are mentioned in MA file.
- **Container closure system**
  The storage container for inactivated poliovirus consists of a bottle made of PC with a closure made of polypropylene copolymer (PPCO), and the inside of closure is composed of a liner made of silicone.

- **Stability of drug substance:**
  Shelf-life: 36 months.
  Storage Conditions: Store at 5 ± 3 ˚C.

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**
  Paralytic poliomyelitis is manifest as acute flaccid paralysis (AFP), and no specific treatment has been known so far. Formulation development was also conducted to optimize the stability and efficacy of the vaccine. A single human dose (0.5 mL) of Sabin Inactivated Polio Vaccine contains 5 D-antigen units, 8 D-antigen units and 16 D-antigen units of inactivated poliovirus types 1, 2 and 3(Sabin strain), respectively.
  The Sabin Inactivated Polio Vaccine is colorless and clear solution filled in a colorless and clear siliconized glass vial. A volume of 3.1 g is filled considering 5 dose use.

  Physicochemical and Biological Properties
  Manufacturing Process Development.
  The final formulation was developed through optimization of the stability and efficacy of vaccine by LG Chem, Ltd.
  Container closure system and their compatibility.
  Sabin Inactivated Polio Vaccine is filled in a siliconized glass vial which can keep sterility and prevent loss of solvent as well as microbial transmission, which is closed with a rubber stopper was selected which can keep sterility and prevent loss of solvent as well as microbial transmission. and an aluminum cap which can prevent moist permeability and loss of solvent.
  Microbiological Attributes.
  To control the microbial contamination during the manufacturing process of Sabin Inactivated Polio Vaccine, tests were performed in the in-process samples and the final lot from the process validation batches.

- **Manufacture of the drug product:**
  -Description of manufacturing process and process controls along with manufacturers and responsibilities.
  Name and Address: LG Chem, Ltd. Osong Plant 151, Osongsaengmyeong 1-ro, Osong-eup, Heungdeok-gu, Cheongju-si, Chungcheongbuk-do, Korea.
  Responsibility: Manufacturing of Sabin Inactivated Polio Vaccine - Batch release and Release testing of Sabin Inactivated Polio Vaccine - Stability testing of Sabin Inactivated Polio Vaccine.

  The drug product is released after the quality control test according to the test items and acceptance criteria.
  -Control of critical steps and intermediates
  The items of in-process control tests and acceptance criteria of Sabin Inactivated Polio Vaccine are well presented.

  - Process validation and / or evaluation.

  Plant-related and product-related process validation is performed and the results are demonstrated in MA file.

- **Product specification:**
  Excipients are tested according to the reference compendia and released if they meet the Specification. For each excipient, the specifications are submitted.

- **Justification of specification:**
  Excipients using in the manufacturing of the Sabin Inactivated Polio Vaccine are in accordance with the Pharmacopoeia and managed according to the specification
- **Characterization of impurities.**
  The impurities derived from the manufacturing process of active ingredients are controlled at the level of drug substance
  Product-related impurities may be various molecular variants derived from the antigens, but they are not controlled specifically as they are generally known to have similar antigenicity to the antigen.
  - **Reference Standards or Materials.**
    The list of reference standard used in release of inactivated poliovirus was submitted & well illustrated.

  - **Container closure system.**
  - The Sabin Inactivated Polio Vaccine is filled in a siliconized glass vial and sealed with a rubber stopper and an aluminum flip-off cap.

- **Stability of the drug product.**
  - Approved Shelf life: 36 months.
  - Storage conditions: Store the finished product at (2-8℃) & **Do not Freeze.**
- **<u>In-USE shelf life and storage conditions</u>:** For multi-dose vials; should be kept between (2-8℃) and used in subsequent immunization sessions for up to 28 days after opening the vial as determined by WHO.

3. Non –clinical aspect:

- Eupolio is Sabin Inactivated Polio Vaccine that contains 5 D-antigen units, 8 D-antigen units and 16 D-antigen units of inactivated poliovirus types 1, 2 and 3 (Sabin strain), respectively as active ingredients. The vaccine should be injected intramuscularly as a dose of 0.5 ml. Poliomyelitis vaccine produces antibodies in the blood ('humoral' or serum immunity) to type I, II and III poliovirus, and in the event of infection, this protects the individual against polio paralysis by preventing the spread of poliovirus to the nervous system. WHO prequalified it for use on *21/12/2020.*
- Human is the only host for the poliomyelitis virus. So, the preclinical program produced supportive data and the reliable efficacy and safety will be withdrawn from clinical data. Toxicological safety considerations were conducted in compliance with Chinese Good Laboratory Practice (GLP) regulations as claimed by the applicant.

- **Pharmacology & pharmacokinetics:**

-The efficacy of LBVC was evaluated by measuring the neutralizing antibody titer for wild virus and Sabin virus using immune serum obtained from rats after single intramuscular administration. The relative potency per DU/dose of LBVC was similar to that of Intravacc's Phase 1/2a clinical sample that showed the potential for clinical success. When comparing the wild virus and Sabin virus challenge to the same immune serum, the relative potency of LBVC with Sabin virus challenge was higher than that with wild virus challenge.

-**Safety pharmacology** studies were conducted in rats and in beagle dogs to evaluate the effect of LBVC on the central nervous system, respiratory function and cardiovascular system. LBVC did not produce significant effects on neurobehavioral function in both male and female rats. Increased body temperature was observed at some measurement time points, but it was not related to the administration of LBVC.

- Pharmacokinetic studies are normally not required for vaccines in accordance with WHO guidelines on non-clinical evaluation of vaccines, Annex 1, TRS No 927.

- **Toxicology:**
  When LBVC was intramuscularly injected as a single-dose into SD rats, no LBVC-related changes in mortality, clinical signs, body weight, organ weight or macroscopic findings were observed.
  In the results of repeated IM injection of LBVC in SD rats, test item-related microscopic changes were observed in the injection sites. Mononuclear cells infiltration, mixed cells infiltration, hemorrhage, myofiber degeneration/necrosis and edema were observed in LBVC treated group and also observed similar or slightly higher in placebo group. The findings were fully reversed after 2-week recovery period. While in NZW rabbits, No LBVC-related changes in clinical signs, body weight, food consumption, body temperature, ophthalmology, coagulation, clinical chemistry, urinalysis or macroscopic findings were observed. Meanwhile, there was no LBVC-related skin reaction during the treatment period. Moreover, intramuscular LBVC administration to NZW rabbits induced local inflammatory reactions at the injection sites or hematological changes.

- **Overall conclusion:** Based on the pharmacology and the toxicology data, Eupolio Inj. is considered acceptable from the preclinical point of view.

4. Clinical aspect:

- The clinical development program consisted of a **two-stage, seamless Phase II/III randomized, double-blind, active-controlled study (LG-VCCL001)** evaluating the safety and immunogenicity of **LBVC** (Sabin strain inactivated poliomyelitis vaccine) compared with **Imovax® Polio** in healthy, full-term infants aged 6–8 weeks.
- **Study Structure**

- **Stage I (Phase II):**
  Dose-finding study comparing **low, middle, and high doses** of LBVC versus Imovax® Polio (N=336).
  Objective: Select optimal LBVC dose based on safety and immunogenicity.
- **Stage II (Phase III):**
  Evaluation of **three manufacturing lots** of the selected LBVC dose (low dose) versus Imovax® Polio (N=1086 randomized).
  Objectives:
  • Demonstrate **lot-to-lot consistency**
  • Demonstrate **non-inferiority in immunogenicity** versus Imovax®
  • Further evaluate safety

- **Clinical Efficacy and Immunogenicity:**

Stage I (Dose-finding)

- All LBVC doses achieved **high seroconversion (97.6–100%)** for Sabin serotypes 1–3 and Wild 3.
- Seroconversion for **Wild 1 and Wild 2** was lower in low and middle dose groups compared with Imovax®, consistent with known higher immunogenicity of IPV toward homologous strains.
- GMTs increased robustly for all serotypes in all groups.
  Conclusion: Low dose provided immunogenicity comparable to control and acceptable safety → selected for Stage II.

Stage II (Confirmatory Phase III)
Seroconversion

- LBVC lots demonstrated:
  • **96–98% seroconversion** for Sabin 1–3
  • **97–99% seroconversion** for Wild 1, Wild 2, Wild 3
- All **95% CIs of seroconversion comparisons fell within −10% to +10%**, confirming:
  • **Lot-to-lot equivalence**
  • **Non-inferiority to Imovax® Polio**

Antibody Titers

- **Higher GMTs** in LBVC for Sabin 1–3 compared with Imovax®
- **Lower GMTs** in LBVC for Wild 1–3 vs. Imovax®, but without clinically relevant differences in seroprotection
- Both vaccines achieved **protective titers** across all serotypes.

Overall Immunogenicity Conclusion:
LBVC demonstrated **robust immune responses**, protection across all serotypes, lot consistency, and **non-inferiority to Imovax® Polio**.

- **Clinical Safety:**

Across both stages:

- **AE and ADR rates** were slightly higher in LBVC groups than Imovax®, primarily due to **mild solicited reactions**.
- Most frequent solicited AEs:
  • **Pain/tenderness** at injection site
  • **Irritability/restlessness**
  • **Drowsiness/sleepiness**
  Majority were **mild** and resolved spontaneously.

Serious Adverse Events

- **No vaccine-related SAEs** reported in either stage.
- **Three deaths** occurred in Stage II (2 in LBVC, 1 in control), all assessed **unrelated** to study vaccines (SIDS, viral myocarditis, pneumonia).

Unsolicited AEs

- Generally similar between LBVC and Imovax®.
- Most common: pyrexia, upper respiratory infections, rhinitis.

Other Safety Findings

- No meaningful differences in **vital signs**, physical examination assessments, or systemic findings across groups.

Safety Conclusion:
LBVC demonstrated a **favorable safety profile**, acceptable tolerability, no safety signals of concern, and no vaccine-related SAEs.

- **Overall conclusion:**

The Phase II/III clinical program demonstrates that **LBVC (low-dose Sabin IPV)** is:

- **Immunogenic**, producing strong seroconversion and protective antibody levels
- **Consistent in manufacturing**, with confirmed lot-to-lot equivalence
- **Non-inferior to Imovax® Polio**, an established inactivated polio vaccine
- **Safe and well tolerated**, with no vaccine-related SAEs or significant safety concerns

Overall, LBVC meets clinical requirements for approval as a safe and effective inactivated poliovirus vaccine for primary immunization in infants.

- **Benefit/ Risk discussion:**

Benefits

- **High seroconversion rates** and **protective antibody titers** across all Sabin and wild poliovirus serotypes.
- **Demonstrated non-inferiority** to an established comparator (Imovax® Polio).
- **Consistent immunogenicity** across three manufacturing lots.
- Suitable for use in routine infant immunization schedules.

Risks

- Slightly higher rate of **mild solicited reactions** compared with Imovax®, but no clinically meaningful safety concerns.
- No vaccine-related SAEs or fatal events.

Benefit–Risk Balance:

The benefit–risk profile of LBVC is **favorable**, as the vaccine delivers strong and effective immunization while demonstrating an acceptable, predictable, and well-tolerated safety profile consistent with established pediatric vaccines.

5. General Conclusion and Recommendations if any:

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