Taiwan Food and Drug Administration

Assessment Report

Trade Name： **"高端"腸病毒71型疫苗/ Envacgen**

Active Ingredient：Inactivated EV71 whole virus

License Number：MOHW-BM 000152

Applicant：高端疫苗生物製劑股份有限公司

Approval Date：112.04.13.

Indication：適用於 2 個月以上至未滿 6 歲嬰幼兒的主動免疫接種，以預防腸病毒 71 型感染所引起之疾病。

Indicated for active immunization for the prevention of disease caused by Enterovirus 71 in children aged 2 months to less than 6 years of age.

1. Background Information

Trade Name	"高端"腸病毒71型疫苗/ Envacgen
Active Ingredient(s)	Inactivated EV71 whole virus
Applicant	高端疫苗生物製劑股份有限公司
Dosage Form & Strengths	注射劑
Indication	適用於 2 個月以上至未滿 6 歲嬰幼兒的主動免疫接種，以預防腸病毒 71 型感染所引起之疾病。 Indicated for active immunization for the prevention of disease caused by Enterovirus 71 in children aged 2 months to less than 6 years of age.
Posology	以肌肉注射的方式將 0.5 ml "高端"腸病毒71型疫苗(Envacgen)注射至手臂或大腿外側，共兩劑，兩劑間隔 56 天。接種第一劑時未滿 2 歲之嬰幼兒，建議於第一劑後一年接種追加劑。
Pharmacological Category **ATC Code**	腸病毒疫苗尚未有編碼。

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Envacgen is an enterovirus 71 (EV71) vaccine contains formaldehyde-inactivated monovalent whole virion of the E59 with the genotype of B4 of EV71 virus. Envacgen is produced in Vero cells. Detailed description of the origin, history, and preparations of cell banks are provided. Adventitious and endogenous agent safety testing, identity, and genetic stability for cell banks and virus seeds were performed. Raw materials of direct and indirect biological origin are also justified. Characterization studies are presented including electron microscope examination and sodium dodecyl sulfate polyacrylamide gel electrophoresis analysis. The exclusion for impurities from routine testing is appropriately justified.

Manufacturing process with in-process controls, process development histories for process versions, comparability studies, process validation, specification, analytical methods and validation, batch analyses, and reference materials are provided to demonstrate the quality of drug substance using commercial process. The stability studies are derived from drug substance batches produced with the commercial process. The applicant commits that the

annual post-approval on-going stability will be tested at least one batch for commercial product.

2.1.2 Drug product

Envacgen is a sterile, preservative-free, single-use pre-filled syringe for injection, packaged in a 1 mL Type I clear glass syringe with needle, plunger rod, and rubber stopper. Each syringe contains 2.5 μg EV71 antigen and 150 μg Aluminum in form of $AlPO_4$ adjuvant in 0.5 mL of phosphate buffer solution. Neither novel excipient nor excipients of human or animal origin are used in the formulation. Drug product manufacturing process and formulation development are described appropriately. Manufacturing process within process controls, process validation, specification, and batch analyses are provided and show that the manufactures of drug product are controlled properly. The stability studies support the shelf life of Envacgen for 18 months under the storage condition of 2-8°C, protect from exposure to light. The applicant commits that the annual post-approval on-going stability will be tested at least one batch for commercial product.

In conclusion, information on the drug substance and drug product is regarded as appropriate to support the quality of Envacgen.

Recommendation for future quality development:
1. A two-tiered reference standard system should be established by using WHO reference reagent (EV71 B4 strain inactivated vaccine 18/156). The in-house reference standards should be calibrated against an international or national reference standard. Re-qualification of in-house reference standards should be performed annually.

2. The leachable study is recommended to continuously monitor the potential leachable impurities under the proposed storage conditions until expiry.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Immunogenicity studies showed that the EV71 vaccine could elicit functional antibodies and was immunogenic in mice and rabbits. Besides, EV71 vaccine could prevent EV71 C4 strain virus-induced death, clinical symptom, and body weight loss in the suckling mice model. The EV71 vaccine provided protection against the challenge of the EV71 C4 strain in SCARB2

transgenic mice. No safety pharmacology studies have been performed since no signs of adverse effects or undesirable pharmacological activity affecting physiological functions were observed in pharmacology or toxicity studies.

2.2.2 Toxicological Studies

In a single-dose toxicity study in rats, no unexpected change was noted except the reversible increment of creatine kinase was observed. In a 35-day repeated-dose toxicity study in rats, no prominent vaccine-related toxicities were noted up to 20 μg total protein/ 600 μg $AlPO_4$ adjuvant. In a 35-day repeated-dose toxicity study in rabbits, the increment of creatine kinase was also noted. Perinerval eosinophil infiltrations in sciatic nerves and inflammatory reactions at the injection site were noted in the vaccinated and adjuvant-alone groups, respectively. Statistical longer in QT and QTc intervals were detected in females in the adjuvant-control group. The high dose tested in the repeated-dose toxicity is 8-fold higher than the total protein dose in the proposed regimen. Atypical trauma induced by i.m. adjuvant injections was observed in both rats and rabbits. The severity and incidence of inflammation within injection sites between the high-dose, low-dose, and adjuvant control groups were not statistically significant. Genotoxicity, carcinogenicity, or developmental and reproductive toxicology studies were not warranted for the EV71 vaccine.

2.3 Clinical Pharmacology Evaluation

NA

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The phase 3, randomized, double-blind, placebo-controlled study CT-EV-31 enrolled infants and children aged from 2 months to less than 6 years from Taiwan and Vietnam. A total of 3061 subjects were randomized. All of them received vaccination on Day 1 and Day 57, and a booster dose was administered on Day 366 for subjects aged from 2 months to less than 2 years.

The CT-EV-31 study had demonstrated a 100% vaccine efficacy against EV71-associated disease; with 22 cases of confirmed EV71-associated diseases in the placebo group and none observed in the Envacgen group. Sequencing of the 21 samples from Vietnam subjects showed that 11 of them were infected with the B5 subgenotype and 10 were C4 subgenotype.

In the immunogenicity substudy CT-EV-31s, the seroprotection rate (defined as a serum

neutralizing antibody (NTAb) titer ≥ 1:32) at 28 days after the first 2 doses of vaccination (Day 85) was 99.5% (95% CI: 98.88, 99.84) in the Envacgen group, with the lower limit of the 95% CI greater than 90%. The seroprotection rate at 6 months after the first 2 doses of vaccination (Day 237) was 97.9% (95% CI: 96.81, 98.67) in the Envacgen group, with the lower limit of the 95% CI greater than 70%.

The NTAb geometric mean titers (GMTs) at Day 85 were compared between Lot 1, Lot 2, and Lot 3 for the evaluation of lot-to-lot consistency. Taking into account the immunogenicity data and clinical performance regarding efficacy and safety results, there were no significant differences between different lots.

2.4.2 Safety Results

In Study CT-EV-31, 3049 subjects received at least one dose of study vaccine. Among them, 1521 subjects were randomized to Envacgen group. The proportion of subjects with solicited AEs, unsolicited AEs, and SAEs were similar between Envacgen and placebo groups. The most frequently reported solicited local AEs were injection site pain, swelling, and erythema. The most frequently reported solicited systemic AEs were fever, fussiness, and decreased appetite. The most frequently reported unsolicited AEs were pharyngitis, nasopharyngitis, and upper respiratory tract infection. In general, the incidence and severity of AEs were similar between treatment groups.

2.5 Bridging Study Evaluation

The Phase 1 clinical trial in healthy adults (CT-EV-1) and Phase 2 dose-ranging trial in children (CT-EV-21) were conducted in Taiwan. The Phase 3 vaccine efficacy trial (CT-EV-31) were conducted in Taiwan and Vietnam, with the majority of subjects (around 80%) enrolled from Vietnam. The disease presentation and circulating subgenotype were similar between Vietnam and Taiwan. No identified intrinsic or extrinsic factor was expected to lead to ethnic difference. Bridging study was not required. The subgroup analyses showed consistent vaccine efficacy and safety profile between Vietnam and Taiwan.

2.6 Conclusion

In conclusion, Envacgen as the active immunization to prevent disease caused by EV71 in children aged from 2 months to less than 6 years demonstrates a favorable risk benefit profile to recommend regular approval. The recommended posology is intramuscular administration as a series of two doses (0.5 mL each) 56 days apart. For children younger than 2 years old, a booster dose one year after Dose 1 was suggested.

3. Post-Marketing Requirements

The Post-authorization Safety Study (PASS) was required to compare the safety profiles between clinical lots.