Taiwan Food and Drug Administration

Assessment Report

Trade Name：安拓伏腸病毒 71 型疫苗 / EnVAX-A71

Active Ingredient：Purified, inactivated Enterovirus 71 virus particles

License Number：MOHW-BM 000149

Applicant ： 安特羅生物科技股份有限公司/Enimmune Corporation

Approval Date：2023/01/18

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.

Background Information

Trade Name	安拓伏腸病毒 71 型疫苗 / EnVAX-A71
Active Ingredient(s)	Purified, inactivated Enterovirus 71 virus particles
Applicant	安特羅生物科技股份有限公司/ Enimmune Corporation
Dosage Form & Strengths	無菌懸浮注射液，每劑 0.5 mL 注射懸浮液，含有不活化之腸病毒 71 型病毒顆粒(不少於 1.5 Unit 的抗原含量)。 Sterile suspension for injection. Each dose contains 0.5 mL suspension of inactivated Enterovirus 71 viral particles (not less than 1.5 Unit of antigen content).
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	詳見仿單/ Please refer to the approved package insert
Pharmacological Category **ATC Code**	N/A

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug Substance

The Drug Substance (DS) consists of formaldehyde-inactivated enterovirus 71 (EV-71) virus particles. To produce DS, EV-71 virus (B4 sub-genotype) is propagated in Vero cells in serum-free medium. At the end of production, the virus suspension is harvested, clarified, and concentrated. The EV-71 virus is further purified and subsequently inactivated by formaldehyde. After inactivation, the DS bulk is sterile filtered into a DS container and then stored at 2-8^{o}C.

The established Vero cell banking system and virus seed lot system have been tested for various adventitious agents and no adventitious agents were found. All compendial and non-compendial raw materials used in the DS manufacturing process have been

justified.

The manufacturing process of DS including in-process controls are described. The process validation reports and analytical procedures validation reports show all results met the requirements. The DS specifications have been provided. The acceptance criteria for host cell DNA and gentamicin were revised for commercial batches. To support the revised specifications, the applicant was requested to provide additional batch analyses as supporting data.

The information of in-house antigen reference standard system has been provided. The applicant was recommended to established two-tiered reference standard system with using national/international reference standard to requalify the in-house antigen reference standard annually.

The DS stability data has been provided to support the claimed shelf life. No significant change in antigen content was observed in the validation batches.

2.1.2 Drug product

The final product (vaccine) is supplied in a Type I glass pre-filled syringe (PFS) with affixed needle and is intended for intramuscular administration. Each PFS contains 0.5 mL of sterile suspension that is comprised of formaldehyde-inactivated EV71 virus (not less than 1.5 Unit antigen content), phosphate buffer (PBS) and aluminum hydroxide adjuvant.

The manufacturing process of Drug Product (DP) consists of the dilution, sterile filtration, formulation with aluminum hydroxide adjuvant, filling and packaging. The DP process validation reports and analytical procedures validation reports show that all results were within the specifications. In order to further ensure the parameters used in sterile filtration are appropriate, the applicant is requested to provide new data of filter validation. For future quality development, the applicant was also recommended to implement additional controls for aluminum hydroxide adjuvant and to evaluate the ratio of adsorption of the antigen to aluminum hydroxide adjuvant for final product.

The primary container of final product is a type I glass (Ph. Eur.) barrel with a fixed needle. The plunger stopper is made of bromobutyl rubber (Ph. Eur. 3.2.9, USP <381>). The claimed shelf life of final product is 12 months based on the stability data and immunological data of phase III trial. The analytical procedures now used have limitations, and the applicant is requested to implement a new stability indicating

method and provide additional stability data.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Immunogenicity studies showed that the EV71 vaccine could elicit functional antibodies and is immunogenic in mice and rabbits. The EV71 vaccine pre-immunization could protect human SCARB2-Transgenic (hSCARB2-Tg) mice from EV71-induced neurological symptoms and death. Besides, antigens generated in roller bottles adjuvanted with $AlPO_4$, in bioreactor adjuvanted with $AlPO_4$, or in bioreactor adjuvanted with aluminum hydroxide adjuvant induced comparable levels of neutralizing antibodies in mice and rabbits. Moreover, the potency study demonstrated that the increase in immunogenicity was proportional to the dose of EnVAX-A71. No safety pharmacology studies have been performed. Nevertheless, there were no signs of adverse effects or undesirable pharmacological activity when EnVAX-A71 was administered in a single dose or multiple doses in the immunogenicity studies in mice.

2.2.2 Toxicological Studies

In a single-dose toxicity study in rats, no unexpected change 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 observed. 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 QT and QTc intervals were detected in females in the adjuvant control group. The overall toxicity profile of the bioreactor-generated EV71 vaccine is comparable to the roller bottle-generated one, regardless of whether the adjuvant was $AlPO_4$ or aluminum hydroxide adjuvant. Atypical trauma induced by intramuscular 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, and 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 pivotal study of EnVAX-A71 is study EV-BR1701. This study is a multi-center, multi-national, randomized, double-blinded, placebo-controlled study. The objective of EV-BR1701 study is to evaluate the immunogenicity, efficacy, and safety after injection of 2 doses EnVAX-A71 vaccine for infant and children aged 2-month-old to 6-year-old.

The EV-BR1701 enrolled subjects from Taiwan (n=1268) and Vietnam (n=2726). The enrollment of Taiwan subjects has been completed, and the enrollment of Vietnam subjects is ongoing. EV-BR1701study comprised two part, the main study and the immunogenicity sub-study. The primary endpoint of the main study is vaccine efficacy, and the result is pending during this application. In this application, the evaluation was based on interim 2 report with immunogenicity data from Taiwan subjects.

Taiwan subjects (n=1268) were randomized in 4:1 ratio to the EnVAX-A71 vaccine group and placebo group. The stratification factor was age (2-month-old to 1-year-old, 1-year-old to 2-year-old, 2-year-old to 3-year-old, and 3-year-old to 6-year-old). Subjects in vaccine group received 2 doses of EnVAX-A71 (D0 and D28), while the placebo group receive adjuvant [$Al(OH)_3$]. There were 316 subjects in the immunogenicity subgroup.

On Day 56, the seroprotection rate (neutralizing antibody titer≧1:32) was 98.31% in the vaccine group and 6.78% in the placebo group. Six months after vaccination (D196), the seroprotection rate (neutralizing antibody titer≧1:32) was 98.28% in the vaccine group and 6.90% in the placebo group. The seroprotection rate fulfills the requirement for accelerated approval.

Infant aged 2-month-old to children aged 6-year-old								
immunogenicity	EnVAX-A71 vaccine group				Placebo [$Al(OH)_3$] group			
	Baseline	Day56	Day196	Day392	Baseline	Day56	Day196	Day392
Subject number	N=237	N=237	N=232	N=230	N=59	N=59	N=58	N=59
Seroprotection* Rate	11 (4.64%)	233 (98.31%)	228 (98.28%)	230 (100.0%)	2 (3.39%)	4 (6.78%)	4 (6.90%)	4 (6.78%)

* Seroprotection: Neutralizing antibody titler≧1:32

2.4.2 Safety Results

The interim 2 report of pivotal study of EnVAX-A71 provided 1-year safety data for 1266 Taiwanese subjects. 1014 subjects received at least one dose of EnVAX-A71 vaccine and 252 subjects received placebo.

After injections, the incidence of local solicited AE was around 30%, and was similar

between vaccine group and placebo group. The most common local solicited AEs in vaccine group were pain (21.57%) and tenderness (17.59%). After injections, the incidence of systemic solicited AE was around 27%, and was similar between vaccine group and placebo group. The most common systemic solicited AEs in vaccine group were fever (10.34%) and decreased appetite (12.52%). Most solicited AEs were mild in severity. Other common unsolicited AEs included nasopharyngitis (14.6% in vaccine group), upper respiratory tract infection (12.3% in vaccine group), and pyrexia (6.8% in vaccine group).

The incidence of special AEs in vaccine group and placebo group was 3.25% and 5.56%, respectively. There were 3 seizure events in vaccine group. Two events were febrile convulsion, and the other one seizure events occurred after a long time after vaccination (3 to 6 months). There was no death event. The incidence of SAE were similar between vaccine group and placebo group (9.1% and 10%). The most common SAE was pneumonia. No SAE were determined to be causally related to vaccination.

2.5 Bridging Study Evaluation

The pivotal study EV-BR1701 was conducted in Taiwan and 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.

2.6 Conclusion

In conclusion, EnVAX-A71 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 accelerated approval. The accelerated approval is based on clinical immunogenicity data and safety data. Further efficacy data in the pivotal EV-BR1701 study is required for regular approval.

3. Post-marketing Requirement

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1. Provide additional batch analyses of drug substance to support the revised specifications for residual host cell DNA and gentamicin.
2. Provide new data of the filter validation to further ensure the process parameters used during the sterile filtration are appropriate.
3. Implement a two-tiered antigen reference standard system with using a national/international reference standard to requalify the in-house antigen reference standard annually.

4. Implement a new stability indicating method for the final product.
5. Provide additional batch analyses and stability data for drug substance and drug product as supportive data to further justify the current specification.
6. Implement additional control(s) for aluminum hydroxide adjuvant.
7. Implement an assay to evaluate the ratio of adsorption of the antigen to aluminum hydroxide adjuvant for final product.

Clinical

1. Final efficacy and safety result of EV-BR1701 study is mandatory for regular approval.
2. Post-Authorization Safety Study (PASS) is required.