Taiwan Food and Drug Administration

Assessment Report

Trade Name：能伏鼻三價鼻噴式流感疫苗 / FluMist Trivalent Flu Vaccine

Active Ingredient：
Each 0.2 mL contains：Three live attenuated influenza virus reassortant strains (H1N1, H3N2, and B/Victoria).

License Number：MOHW-BI 001286

Applicant：臺灣阿斯特捷利康股份有限公司

Approval Date：2025/03/24

Indication：
適用於 2 歲以上至未滿 18 歲兒童及青少年之主動免疫接種，以預防此疫苗所涵蓋之 A 型與 B 型流感病毒所引起的流感。

For active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine, for persons 2 through <18 years of age.

Background Information

Trade Name	能伏鼻三價鼻噴式流感疫苗 / FluMist Trivalent Flu Vaccine
Active Ingredient(s)	Each 0.2 mL contains: Three live attenuated influenza virus reassortant strains are A/Norway/31694/2022 (H1N1, A/Victoria/4897/2022-like), A/Norway/16606/2021 (H3N2, A/Darwin/9/2021-like), B/Austria/1359417/2021 (Victoria Lineage),
Applicant	臺灣阿斯特捷利康股份有限公司
Dosage Form & Strengths	鼻用噴液懸浮劑 0.2 mL
Indication	適用於 2 歲以上至未滿 18 歲兒童及青少年之主動免疫接種，以預防此疫苗所涵蓋之 A 型與 B 型流感病毒所引起的流感。 For active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine, for persons 2 through <18 years of age.
Posology	詳如仿單。
Pharmacological Category **ATC Code**	J07BB03

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug Substance

General Information of Drug Substance (DS)

The FluMist Trivalent is a seasonal live attenuated influenza vaccine (T/LAIV) that consists of three different cold-adapted (*ca*) , temperature sensitive (*ts*) and attenuated (*att*) vaccine virus：two influenza Type A strains (H1N1 and H3N2), and one influenza Type B strains (Victoria lineage). The haemagglutinin (HA) and neuraminidase (NA) proteins are key epitopes that induce the major protective immune response in human. The Master Virus Seeds (MVS) used in LAIV is prepared in Specific Pathogen Free (SPF) eggs by using the reverse genetics method to produce the genetic reassortant between the wild-type influenza virus (HA and NA antigens) and cold-adapted master donor virus (other proteins). Thus, the reassortant vaccine strains derive their antigenic phenotypes from the wild-type strain recommended by the World Health Organization (WHO), and their cold-adapted, temperature-sensitive, and attenuated phenotypes from the master donor virus.

Manufacture

T/LAIV DS includes the monovalent pooled harvest (MPH) from each of three influenza strains, and is manufactured at MedImmune UK Limited. The manufacturing process and control strategy of LAIV monovalent bulk (MB) are included in the dossier. The critical process parameters (CPP), key operating parameters (KOP), in-process controls (IPC) were established to ensure consistent manufacturing. Materials of animal origin used during the manufacture of T/LAIV DS have been identified, and appropriate information states that all meet the regulatory requirements. The proposed process validation is acceptable to ensure the quality of T/LAIV monovalent bulk DS. Several changes have been implemented in the T/LAIV DS manufacturing process. The comparability studies demonstrate that the quality of DS manufactured from different process are comparable.

Characterization

A series of analytical methodologies applied for monovalent bulk DS characterization are capable of evaluating biological, physical, genetic, and biochemical properties. The potential egg-related impurities, and process-related impurities have been evaluated appropriately. Overall, the results support that T/LAIV DS has the expected structure, relative biological activity, and the impurities are well controlled.

Control of Drug Substance

The specifications of pooled harvest fluid and monovalent bulk DS are well justified.

Compendial and non-compendial analytical procedures used for release and stability testing have been well qualified. Batch analysis and Certification of Analysis (CoA) of representative batch have demonstrated that all data met the acceptance criteria. Overall, the information provided is sufficient to demonstrate the consistency of the T/LAIV DS manufacturing process capabilities.

Stability

The sufficient long-term statistical stability data support that all quality attributes are expected to remain within the acceptance criteria at the recommended storage condition.

2.1.2 Drug Product

Description of Drug Product (DP)

T/LAIV DP is a sterile liquid composed of three serotypes (A/H3N2, A/H1N1, and B/Victoria) and combined with sucrose, phosphate buffer, gelatin, arginine, monosodium glutamate and Water for Injection (WFI). The final product is presented as a 0.2 ml nasal sprayer.

Pharmaceutical Development and Manufacture

T/LAIV DP is manufactured at AstraZeneca Pharmaceuticals LP, USA. The sufficient information illustrates that the processes of T/LAIV and Q/LAIV are comparable. The overall manufacturer process, process controls and parameters are described in details, and process validation results demonstrate the robustness and consistency of the DP manufacturing process.

Control of Drug Product

The specification of T/LAIV DP has been established, the analytical procedures have been appropriately validated, and the acceptance criteria are thoroughly justified. Batch release results and CoAs further confirm the consistency of quality.

Stability

Based on the comprehensive stability studies, T/LAIV DP shelf-life is well justified when stored at 2 ~ 8°C in container closure system.

Overall, the CMC quality data, including the manufacturing process, control strategy, characterization, specifications, container closure system, and stability, support that the manufacturing of FluMist T/LAIV is well-controlled and demonstrates consistent quality.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

FluMist contains live attenuated influenza virus reassortant strains, which were cold-adapted and temperature-sensitive. The characteristics induce the virus strains replication in the nasopharynx and the protective immunity. Therefore, FluMist is formulated as nasal spray suspension.

To assess the distribution and clearance of the nasal spray formulations, Study PPL-1014 was conducted. The healthy subjects received refrigerated and frozen vehicle formulations of FluMist, and the most different from the 2 formulations above was dosing volume (0.5 mL for the frozen vehicle, and 0.2 mL for the refrigerated vehicle). After administration of the 2 vehicle formulations, the majority of the deposition region was nasal cavity, the targeted site inducing the activity of the virus reassortant strains. And the refrigerated vehicle formulation was deposited in the nasal cavity more than the frozen vehicle (mean values 76.3% versus 48.6%, respectively). It might be due to fact that the larger administration volume of frozen vehicle resulted in smaller median droplet size with more deposition in the lower airways and lungs. On the other hand, less dispositions were observed in esophagus and stomach with the refrigerated vehicle formulation than those observed with the frozen vehicle formulation, indicating that partial fluid from the nasal cavity drained into the oropharynx with subsequent swallowing of the fluid.

For the properties of clearance, the mean (%CV) $T_{1/2}$ in nasal cavity was determined to be 0.37 (113.5) and 0.44 (109.1) hours for the frozen and refrigerated vehicles, respectively. The rapid removal of vehicles from the nasal cavity results mainly from the effects of mucociliary clearance.

2.3.2 Interaction Studies

As the active ingredients of FluMist is live attenuated influenza virus reassortant strains, no PK-related drug-drug interaction was expected.

2.3.3 Special Populations

As the active ingredients of FluMist is live attenuated influenza virus reassortant strains, the PK properties of FluMist in renal impairment subjects was considered similar to that in subjects with normal renal function.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

A total of 9 pediatric studies and 5 adult studies were designed to assessed efficacy of T/LAIV. Study MI-CP111, D153-P501, D153-P502, D153-P504, D153-P513, D153-P514, D153-P515, and D153-P522 were pediatric trials.

When comparing VE, seven out of the nine pediatric trials carefully evaluated were passed: 92.6% (95% CI: 87.3, 95.7) in AV006 (Children 15-71 M; vs PBO); 72.9% (95% CI: 62.8, 80.5) in D153-P501 (Children 12 to < 36 M; vs PBO); 85.4% (95% CI: 74.3, 92.2) in D153-P502(Children 6 to < 36 M; vs PBO); 73.5% (95%CI: 63.6, 81.0) in D153-P504 (Children 6 to < 36 M; vs PBO); 44.5% (95% CI: 22.4, 60.6) in MI-CP111 (Children 6-59 M; vs active control); 34.7% (95% CI: 3.9, 56.0) in D153-P515 (Children with asthma 6 to < 18 year of age; vs active control); 42.3% (95% CI: 21.6, 57.8) in D153-P507 (Adults >= 60 year of age; vs PBO); where M=months.

2.4.2 Safety Results

Safety data derived from over 49000 participants who have received the T/LAIV (frozen T/LAIV or refrigerated T/LAIV) in 42 clinical trials. In the Pooled T/LAIV Pediatric Population, a total of 28,873 participants 2 to 17 years of age received T/LAIV and contributed data to the pooled analysis for Year 1, and a total of 11,007 participants received 2 doses. A total of 9,386 participants received refrigerated T/LAIV, and the remainder received the frozen formulation of T/LAIV. The most common solicited event after Dose 1 was runny/stuffy nose, which had the greatest risk difference among all symptoms compared to the control group (TIV or placebo). The frequency of any solicited event after Dose 2 was lower than or similar to that after Dose 1. Fever equal to or over 40 ℃ was uncommon (<0.5%). Common AEs were collected during Days 0 to 10 post dose. In TIV-controlled studies, 20.7% of T/LAIV participants and 18.1% of TIV participants in the Pooled T/LAIV Pediatric Population reported ≥ 1 AE after Dose 1, and 16.1% of T/LAIV participants and 16.0% of TIV participants reported ≥ 1 AE post Dose 2. In Year 1 of placebo-controlled studies, 29.7% of T/LAIV participants and 27.6% of placebo participants reported ≥ 1 AE after Dose 1, an 24.3% of T/LAIV participants and 26.5% of TIV participants reported ≥ 1 AE post Dose 2. The percentage of events post dose in Year 2 of placebo-controlled studies was comparable to that observed post Dose 2 in Year 1. "Rhinorrhea" was the preferred term with a higher frequency than the control group after any dose of T/LAIV. A majority of AEs was mild in intensity. During Days 0 to 42 post last dose, SAEs were reported for 129/28,873 (0.45%) participants administered T/LAIV in Year 1 and 24/8,037 (0.30%) participants

administered T/LAIV in Year 2 for the Pooled T/LAIV Pediatric Population. No cases of encephalitis, encephalopathy, facial palsy, hemolytic uremic syndrome, Guillain-Barré syndrome, arthritis, or toxic epidermal necrolysis were reported for participants 2 to 17 years of age who received T/LAIV.

Nine deaths were reported in participants < 18 years of age who received T/LAIV in clinical studies. The causes of death collected in all trials have small numbers and lack of temporal relationship, and are more reflected to diseases or accidental events that are known in each age group. No death was considered by the investigator or medical monitor to be related to T/LAIV.

2.5 Bridging Study Evaluation

This BSE application (Flumist T/LAIV) uses the same dataset as Flumist Q/LAIV. Please refer to the Assessment Report of Flumist Q/LAIV.

2.6 Conclusion

Based on the review of data on quality, non-clinical pharmacology/toxicology, safety and efficacy, CDE considers that the benefit-risk balance of “FluMist Trivalent Flu Vaccine” is favorable in the following indication: for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine, for persons 2 through <18 years of age.

3. Post-Marketing Requirements

Nil