Taiwan Food and Drug Administration

Assessment Report

Trade Name：
安泰適注射劑 1 毫克 / IMDELLTRA for Injection 1 mg
安泰適注射劑 10 毫克 / IMDELLTRA for Injection 10mg

Active Ingredient：Tarlatamab

License Number： MOHW-BI 001281、MOHW-BI 001282

Applicant：台灣安進藥品有限公司

Approval Date：2025/02/26

Indication：
適用於治療使用含鉑化學治療期間或之後疾病惡化之擴散期小細胞肺癌 (ES-SCLC) 的成年病人。

此適應症係依據腫瘤整體反應率及反應持續時間加速核准。
此適應症仍須執行確認性試驗以證明其臨床效益。

The treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Background Information

Trade Name	安泰適注射劑 1 毫克/ IMDELLTRA for Injection 1 mg 安泰適注射劑 10 毫克/ IMDELLTRA for Injection 10mg
Active Ingredient(s)	Tarlatamab
Applicant	台灣安進藥品有限公司
Dosage Form & Strengths	凍晶注射劑 1mg/vial 凍晶注射劑 10mg/vial
Indication	IMDELLTRA 適用於治療使用含鉑化學治療期間或之後疾病惡化之擴散期小細胞肺癌 (ES-SCLC) 的成年病人。 此適應症係依據腫瘤整體反應率及反應持續時間加速核准。此適應症仍須執行確認性試驗以證明其臨床效益。 The treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).
Posology	詳見仿單
Pharmacological Category **ATC Code**	L01FX33

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance (DS)

Tarlatamab is a bispecific DLL3-directed CD3 T-cell engager that binds to DLL3 expressed on the surface of cells, including tumor cells, and CD3 expressed on the surface of T cells. Tarlatamab is produced using recombinant DNA technology in Chinese hamster ovary cells. It consists of 982 amino acids and has a molecular weight of approximately 105 kilodaltons. The preparation, testing and characterization of the cell banks have been provided in sufficient details to demonstrate the suitability and quality of cell banks for the DS production. Sufficient information on the materials used in the manufacture of DS have been provided, including the acceptance criteria for non-compendial raw materials.

A flow diagram of DS manufacturing processes is provided, along with in-process controls, operating ranges, and limits. Process validation has been successfully completed for the commercial DS manufacturing. Comparability results illustrated that batches through manufacturing development show no significant impact on DS quality attributes. Characterization studies are presented including primary and high order structure, structure, charge and size heterogeneity, and biological activity analyzed by cell-based assays. Process-and product-related impurities are also well-characterized and appropriately controlled at acceptable levels. The specification of DS is provided within justifications. Batch results are within acceptable criteria to demonstrate DS quality consistency. The DS shelf-life for recommended storage condition is proposed and stability results are considered sufficient to support the intended shelf-life.

2.1.2 Drug product (DP)

IMDELLTRA 1 mg or 10 mg is supplied with lyophilized powder in a single-dose vial for reconstitution and further dilution. Each 1 mg vial contains Tarlatamab (1 mg), after reconstitution with 1.3 mL of Sterile Water for Injection the resulting concentration is 0.9 mg/mL IMDELLTRA. Each 10 mg vial contains Tarlatamab (10 mg), after reconstitution with 4.4 mL of Sterile Water for Injection the resulting concentration is 2.4 mg/mL IMDELLTRA. IV Solution Stabilizer (IVSS) is supplied in a single-dose vial, preservative-free, colorless to slightly yellow, clear solution. Formulation development and comparability studies are performed through pharmaceutical development and compatibility of the container closure system with the dosage form is assessed. The manufacturing process performance and robustness is demonstrated during process validation. The batch release results with CoAs are

within the DP specification. The shelf-life of DP and IVSS for recommended storage condition is proposed and stability results are considered sufficient to support the intended shelf-life.

Overall, the quality results include the manufacturing process, control of materials, in-process controls, characterization, specifications, container closure system, and stability. These results adequately support that the manufacturing of DP is well-controlled and quality consistency.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Pharmacology data demonstrated that tarlatamab binds to DLL3-expressing tumor cells and CD3-positive T cells, triggering T-cell activation, expansion, cytokine production, and the release of perforin and granzyme to induce tumor cell apoptosis. In orthotopic and patient-derived xenograft models of small cell lung cancer (SCLC) in NSG mice, tarlatamab exhibited potent antitumor activity, requiring the presence of both DLL3-expressing target cells and CD3-positive T cells. Safety pharmacology assessments incorporated into toxicology studies revealed no undesirable effects on cardiovascular, respiratory, renal, or central nervous systems.

2.2.2 Toxicological Studies

In a pivotal 3-month repeated-dose monkey toxicity study, tarlatamab-related effects included a minimal decrease in lymphocytes at 4500 μg/kg and minimal to mild mononuclear cell infiltrates in the pituitary gland at ≥ 50 μg/kg, with no evidence of tissue injury. The HNSTD was 4500 μg/kg, providing a margin of 7 based on body surface area calculations. Reproductive and developmental studies using a murine surrogate show no maternal toxicity, embryotoxicity, or teratogenicity. The absence of genotoxicity and carcinogenicity studies is agreed since tarlatamab is not expected to interact with DNA or to be carcinogenic. Tarlatamab was well tolerated following IV administration.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Tarlatamab pharmacokinetic parameters are presented as geometric mean (CV%) unless otherwise specified. The exposure of tarlatamab increased dose proportionally in the evaluated dose range of 1 mg to 100 mg every 2 weeks (10 times the highest approved recommended dosage). Tarlatamab steady state exposures were achieved by Cycle 2 Day 15.

Based on the population PK analysis, concentration-time profiles for each patient were simulated following the clinical regimen of 1 mg on Day 1, 10 mg on Days 8 and 15, and 10 mg every two weeks (Q2W) thereafter. PK parameters were summarized after the first step-up dose, the first treatment dose, and at steady state, as shown below. After the first step-up dose of 1 mg, the geometric mean (% CV) Cavg of tarlatamab is 102 ng/mL (29%), Cmax is 285 ng/mL (41%), and Ctrough is 47 ng/mL (38%). Following the first treatment dose of 10 mg, the geometric mean (% CV) Cavg of tarlatamab is 1050 ng/mL (29%), Cmax is 2900 ng/mL (41%), and Ctrough is 502 ng/mL (39%). At steady state with a 10 mg Q2W regimen, the geometric mean (% CV) Cavg of tarlatamab is 1040 ng/mL (44%), Cmax is 3400 ng/mL (40%), and Ctrough is 495 ng/mL (73%).

Based on the population PK analysis, geometric mean (%CV) of tarlatamab volume of distribution at steady state (Vss) were estimated to be 8.6 L (18.3%). No dedicated metabolism studies were performed. Tarlatamab is expected to be metabolized into small peptides by catabolic pathways. Tarlatamab's median terminal elimination half-life (min, max) is 11.2 (4.3 to 26.5) days and the estimated systemic clearance is 0.65 L/day (44%) in patients with SCLC.

2.3.2 Interaction Studies

No formal clinical drug-drug interaction studies were performed. As an IgG tarlatamab is expected to be biotransformed in the same manner as any other endogenous IgG (degraded into small peptides and amino acids via catabolic pathways) and is subject to similar elimination. Renal excretion and hepatic enzyme-mediated metabolism of intact tarlatamab are therefore unlikely to represent major elimination routes. As such, variations in renal and hepatic function or drug metabolizing enzymes are not expected to affect the elimination of tarlatamab.

However, initiation of IMDELLTRA treatment causes transient release of cytokines that may suppress CYP450 enzymes and may result in increased exposures of concomitant

CYP substrates. In patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, monitor for known adverse events. Adjust the dose of the concomitant drug as needed.

2.3.3 Special Populations

Based on cross-study population PK analyses, tarlatamab PK parameters were not impacted by age or sex. Body weight was found to be correlated with tarlatamab clearance, with increase in body weight associated with increase in clearance. This difference in exposure is not expected to be clinically relevant as confirmed by subgroup analyses of efficacy as assessed by confirmed objective response rate (ORR) or disease control rate (DCR) in subjects with low and high body weight categories. In summary, no clinically significant differences in the pharmacokinetics of tarlatamab were observed based on age (32 to 82 years), sex (64% male) and body weight (35 to 149 kg).

Like other biologic therapeutics, owing to its large molecular size (~105 KDa), tarlatamab is expected to be degraded into small peptides and amino acids via catabolic pathways. Tarlatamab is neither expected to be metabolized by hepatic drug metabolizing enzymes nor undergo renal glomerular filtration and excretion. Based on the population PK analyses, the mild hepatic impairment (based on National Cancer Institute criteria) and mild or moderate renal impairment (based on eGFR) were not correlated with tarlatamab clearance. In summary, no clinically significant differences in the pharmacokinetics of tarlatamab were observed based on mild or moderate renal impairment (eGFR $\geq$ 30 to < 90 mL/min), or mild hepatic impairment (total bilirubin $\leq$ upper limit of normal (ULN) and AST > ULN). The effects of severe renal impairment (eGFR 15 to 29 mL/min), end-stage renal disease (eGFR <15 mL/min), or moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN, any AST) on the pharmacokinetics of tarlatamab are unknown.

In Study DeLLphi-301, of the patients who received recommended step-up and full dosage of IMDELLTRA and were evaluable for presence of ADA against tarlatamab, 3.2% (4/124) of patients tested positive for anti-tarlatamab antibodies and none of the patients developed neutralizing antibodies against tarlatamab. Because of the low occurrence of ADA, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and effectiveness of tarlatamab is unknown.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Study DeLLphi-301 was reviewed to evaluate the efficacy of IMDELLTRA (tarlatamab) indicated for the following indication.

"IMDELLTRA 適用於治療使用含鉑化學治療期間或之後疾病惡化之擴散期小細胞肺癌(ES-SCLC) 的成年病人。

此適應症係根據整體反應率和反應持續時間獲得加速核准。此適應症的持續核准可能取決於確認性試驗中臨床效益的驗證和描述。"

The treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continuedapproval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

The recommended dosing regimen is as follows.

- An initial dose of 1 mg on Day 1 followed by 10 mg on Days 8, 15, and every 2 weeks thereafter.

Study DeLLphi-301 is a Phase 2, open-label study in patients with recurrent SCLC who had progressed or recurred following 1 platinum-based regimen (with or without immune checkpoint inhibitor) and at least 1 other line of therapy (re-treatment with a platinum-based regimen was considered a second line of therapy).

Overall, 220 subjects received at least 1 dose of tarlatamab, including 99 subjects in the 10 mg target dose group across Parts 1 and Part 2, 87 subjects in the 100 mg target dose group in Part 1, and 34 subjects in the Part 3 modified safety monitoring 10 mg target dose group. As of the primary data cutoff date (27 June 2023), 149 subjects (67.1%) discontinued tarlatamab. The most frequent reason for discontinuation was disease progression (46.8%).

Of the 99 subjects in the 10 mg target dose group across Parts 1 and Part 2, most were white (57.6%) and men (71.7%). The median (range) age was 64 (35 to 82) years. Overall, subjects had a median of 2 prior lines of therapy, including prior PD-1 or PD-L1 (73.7%) and prior radiotherapy (77.8%). Time to progression after first-line platinum therapy was < 90 days for 27 subjects (27.3%), ≥ 90 to < 180 days for 22 subjects (22.2%), ≥ 180 days for 20 subjects (20.2%), and unknown for 30 subjects

(30.3%). Most subjects had metastatic disease (98.0%), with no brain metastases (77.8%) or liver metastases (61.6%), and an ECOG score of 1 (73.7%).

As of data cutoff date of 27 June 2023, the objective response rate (ORR) as assessed by BICR (97.5% CI) was 41.4% (30.3%, 53.2%) for subjects who received the 10 mg target dose and 32.6% (21.6%, 45.0%) for subjects who received the 100 mg target dose. In the 10 mg target dose group, the median (range) time to response was 1.4 (1.1 to 2.8) months and the median duration of response (DOR) was not reached (95% CI: 5.9, NE) months. The median PFS was 4.3 months (95% CI: 3.0, 5.6)

Updated efficacy data from January 12, 2024 demonstrated an ORR of 40% (95% CI: 30.3-50.3%) for the 10 mg dose, with a median DOR of 9.7 months (95% CI: 6.9, NE) and a median PFS of 4.3 months (95% CI: 2.9, 5.6).

2.4.2 Safety Results

Overall, the safety profile of the 10mg group was better than the 100 mg group. In the 10mg group, most of the TEAEs were <= grade III and the rates for grade 4 TEAEs were 16.2%. The SAE rate was 58.6%. The proportion of patient with AE leading to tarlatamiab discontunuation was 7.1%.

The risk of tarlatamab in patients with relapsed SCLC included CRS (55% of patients receiving tarlatamab), Neurologic toxicity including ICANS(47%), Cytopenia (including neutropenia, thrombocytopenia, and anemia), Infections (41%), Hepatotoxicity(2.1%), Hypersensitivity, Embryo-Fetal Toxicity.

2.5 Bridging Study Evaluation

The properties of tarlatamab are less likely to be sensitive to ethnic factors according to Appendix D in ICH E5 guideline. Meanwhile, there was no clinically meaningful difference in exposures or PK parameters between East Asian subjects (Korean, Taiwanese and Japanese) and Caucasian subjects with SCLC at the proposed dosing regimen of 10 mg Q2W based on cross study comparation and population PK analysis. Thus, tarlatamab showed none to minimally ethnically sensitive in PK's aspect.

The East Asian sites in DeLLphi-301 included Japan, Korea, Singapore and Taiwan. There were 41 participants (41.4%) in the subgroup of Asian Region at the 10mg Cohort. Asian subgroup (regardless of sort by race or region) showed ORR of 48.8% (95%CI: 32.9, 64.9). The safety profile of Asian subgroup was similar to the White subgroup, regardless of pooled populations.

2.6 Conclusion

This multidisciplinary review recommends accelerated approval for IMDELLTRA for Injection 1 mg and 10 mg (Tarlatamab) indicated for the treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

3. Post-Marketing Requirements

Conduct a multicenter randomized clinical trial intended to verify and describe the clinical benefit of tarlatamab in patients with ES-SCLC who have had disease progression on or after platinum-based chemotherapy**.**