Taiwan Food and Drug Administration

Assessment Report

Trade Name：泰莎樂注射液劑 210 毫克 /
TEZSPIRE Solution for Injection 210 mg

Active Ingredient：Tezepelumab

License Number：MOHW-BI 001215

Applicant：臺灣阿斯特捷利康股份有限公司/
AstraZeneca Taiwan Limited

Approval Date：112/2/1

Indication：
12 歲以上嚴重氣喘病人的附加維持治療(add-on maintenance therapy)。使用限制：不適用於緩解急性支氣管痙攣或重積性氣喘(status asthmaticus)。

TEZSPIRE is indicated as an add-on maintenance treatment in patients with severe asthma aged 12 years and older.
Limitation: no indicated for the relief of acute bronchospasm or status asthmaticus.

Background Information

Trade Name	泰莎樂注射液劑 210 毫克 / TEZSPIRE Solution for Injection 210 mg
Active Ingredient(s)	Tezepelumab
Applicant	臺灣阿斯特捷利康股份有限公司/ AstraZeneca Taiwan Limited
Dosage Form & Strengths	注射液劑 210mg/Pre-filled syringe or pen
Indication	12 歲以上嚴重氣喘病人的附加維持治療(add-on maintenance therapy)。使用限制：不適用於緩解急性支氣管痙攣或重積性氣喘(status asthmaticus)。 TEZSPIRE is indicated as an add-on maintenance treatment in patients with severe asthma aged 12 y ears and older. Limitation: no indicated for the relief of acute bronchospasm or status asthmaticus.
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Pharmacological Category ATC Code	R03DX11

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Tezepelumab is a humanized immunoglobulin G2λ (IgG2λ) monoclonal antibody binding selectively to the human thymic stromal lymphopoietin (TSLP), produced from Chinese hamster ovary (CHO) cells. Tezepelumab has a molecular weight of approximately 147 kDa. Tezepelumab binds to human TSLP could prevent its interaction with the heterodimeric TSLP receptor.

Manufacturing

The tezepelumab DS is manufactured in accordance with GMP. The manufacturing process of DS consists of cell culture, harvest, purification, and buffer-adjustment. A production run begins with WCB vial thawed, through the cell culture expansion and harvest of the production culture, followed by purification by a series of chromatography steps. Additional steps are introduced for inactivation/removal of the potential viral contaminants. The DS solution is then adjusted and filtered into storage container.

Controls

- Sufficient details are provided on the source and history of the cell substrate. The generation of the production cell line and the expression vectors is described in detail.
- The details of raw and starting materials used in the manufacturing process as well as quality standards (compendial monograph or in-house specifications) are presented.
- The in-process controls and critical process parameter are provided sufficiently.
- The results of the virus clearance study, and the estimated safety margin retroviral contamination per dose is considered acceptable.
- The risk for transmission of TSE/BSE is inferred to be negligible.
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Process validation

The validation of the manufacturing process was carried out on full-scale PPQ lots. Results obtained from these batches meet the pre-defined criteria and demonstrate the process consistency.

Characterization

The followings are included in characterization studies：

- Physicochemical characterization: primary structure, glycosylation, size variants, disulfide structure, charge variants and higher-order structure.
- Biological characterization: receptor-ligand binding assay and the cell-based bioassay.
- The potential produced- and process-related impurities have been analyzed and are considered sufficiently controlled.
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DS specification

The release testing of the DS includes identity, appearance, purity, potency, and microbiological attributes. Reports of the non-compendial analytical procedures validations are provided. The proposed specifications of DS are considered adequate and acceptable.

Reference materials

The qualification reports of current RSs have been provided.

Stability

The stability data from production batches revealed that the DS is stable under storage condition for 48 months at −30±10°C.

2.1.2 Drug product

TEZSPIRE is available as a sterile 110 mg/mL concentrate for solution in prefilled syringe subassembly (PFS-SA) assembled into an accessorized prefilled syringe (APFS) or a prefilled autoinjector/pen (AI/Pen). The excipients for DP solution contain Glacial acetic acid, L-proline, Polysorbate 80, Sodium hydroxide, and water for injection.

Manufacturing

The manufacturing process consists of DS thawing, mixing the DS with a formulated excipient solution, bioburden reduction, sterile filtration, followed by an aseptic filling into sterile APFS. Then, the DP PFS-SA are assembled into TEZSPIRE APFS or AI/Pen forming a single integral unit.

Controls

The critical process parameters and in-process control tests have been provided properly.

Process validation and/or evaluation

The process validation summaries on three consecutive production batches are provided. The aseptic processing and the suitability of the equipment are ensured.

DP Specification

The release testing of the DP includes identity, appearance, purity, osmolality, potency, pH, particulate matter, microbiological attributes, and deliverable volume. The proposed specifications of DP are considered adequate and acceptable. Batch analysis data of finished product batches are provided, and the results reveal a satisfactory batch to batch consistency.

Reference materials

The qualification reports of current RSs have been provided.

Stability of the DP

The long-term, accelerated, and stressed stability data for DP are provided.

The photo-stability, temperature cycling studies, and transport simulation study were also performed on DP batches. Overall, the stability data provided could support the proposed shelf-life of 36 months when the DP is stored at the recommend condition (5±3°C) and the solid paperboard carton could provide adequate protection from light. The in-use stability results showed that the DP are stable for 30 days at room temperature (20°C - 25°C).

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Tezepelumab inhibited the binding of recombinant human TSLP to the heterodimeric TSLP receptor with a K_I value of 28.7 pM. Tezepelumab bound to human and monkey TSLP with a K_D of 15.8 and 32.2 pM, respectively; on the other hand, tezepelumab did not bind to mouse, rat, or rabbit TSLP. Tezepelumab inhibited TSLP-mediated STAT5 phosphorylation. An anti-mouse TSLP surrogate mAb, M702, was developed to evaluate its pharmacologic properties to mouse TSLP. In an ovalbumin-induced asthma model, M702-treated mice showed decreased airway inflammation as evidenced by histologic changes, BALF cellularity and airway hyperresponsiveness to methacholine challenge. In an intranasal administration TSLP challenge model, the phenotype induced by TSLP was attenuated by anti-TSLP mAb or anti-IL-4Rα mAb.

In a safety pharmacology study in monkeys, no treatment-related effects on cardiovascular function, respiratory rate, neurological behavior, and body temperature were noted up to the highest dose. Furthermore, no tezepelumab-related adverse findings were detected in repeated-dose toxicity studies in monkeys up to the highest doses examined.

2.2.2 Toxicological Studies

In a 6-month repeated-dose toxicity study, no adverse changes were noted up to 300/50 mg/kg/week (the highest doses examined) via the subcutaneous/intravenous route. Anti-drug antibodies were detected in several animals during the dosing and/or recovery phase. Although fertility function was not directly measured, no adverse changes in fertility organs were noted in the 6-month IV and SC toxicity study in sexually mature monkeys.

In an enhanced pre- and postnatal development study in monkeys, no adverse maternal, fetal, or neonatal effects were noted up to 300 mg/kg/week (the highest dose examined). According to ICH S6(R1) guidance, it is acceptable that no genotoxicity studies were conducted with tezepelumab. A weight of evidence evaluation was provided to support the low carcinogenic risk of tezepelumab. In rabbits, administration of tezepelumab as a single IV bolus injection at a dose level of 70 mg/dose site was locally well-tolerated and resulted in no local irritation. In a tissue cross-reactivity study, specific staining was not detected in the examined human or monkey tissue panels.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The PK of tezepelumab were dose-proportional following administration of SC doses ranging

from 2.1 mg to 420 mg. Following SC administration, the C_{max} was reached in a median t_{max} of approximately 3 to 10 days. The absolute bioavailability was estimated to be 77%.

Based on population PK analysis, serum tezepelumab concentrations approached steady state by 12 weeks, with a mean accumulation ratio of 1.86-fold following 210 mg SC Q4W dosing and the estimated central and peripheral volumes of distribution (V_c and V_p) of tezepelumab were 3.91 L and 2.17 L, respectively. Moreover, the estimated CL for tezepelumab was 0.172 L/day for a 70 kg individual, and the elimination half-life was 25.5 days.

Tezepelumab is a human mAb that is degraded by proteolytic enzymes widely distributed in the body. Tezepelumab is not metabolized by hepatic enzymes.

2.3.2 Interaction Studies

As a typical mAb, tezepelumab is not primarily cleared via hepatic pathways. The potential for clinically relevant DDI involving tezepelumab either as a victim or perpetrator is assessed to be low for patients with severe asthma. No PK drug interaction studies were performed with tezepelumab.

Population PK analysis showed that commonly co-administered asthma medications (leukotriene receptor antagonists, theophylline/aminophylline, and oral corticosteroids) had no statistically significant impact on tezepelumab PK in subjects with asthma.

2.3.3 Special Populations

In the final population PK model, body weight, inhaled corticosteroids (ICS) dose level (no/low versus medium/high dose), race (Asian versus non-Asian), formulation, and age were identified as statistically significant covariates on the PK of tezepelumab. Based on population PK analysis, there was no clinically meaningful age-related difference in tezepelumab PK between adolescents and adults.

Other covariates evaluated – including sex, Japanese ethnicity, geographic region, BMI group, CL_{CR}, eGFR, renal function categories, AST, ALT, and total bilirubin, disease status, baseline biomarkers (blood eosinophil counts, FeNO, and total serum IgE), ADA, common asthma concomitant medications, and smoking history – did not show statistically significant impact on the PK of tezepelumab.

Based on the population PK, as well as relevant efficacy, safety, and exposure-response analysis results, it is concluded that there was no clinically relevant effect of age (12 years and above), sex, race, region, weight, BMI, renal or hepatic impairment, disease severity, baseline biomarkers, concomitant asthma medications, and smoking history on the PK of tezepelumab

at the dose of 210 mg SC Q4W. Therefore, no dose adjustment is required for these factors.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

In this submission, three pivotal studies (Studies [PATHWAY], [NAVIGATOR], and [SOURCE]) are provided to support the efficacy of 210 mg of TEZSPIRE SC Q4W as an add-on maintenance treatment in patients with severe asthma aged 12 years and older. The key efficacy results are summarized below.

- ***Study [CD-RI-MED9929-1146] ([PATHWAY]):***

[PATHWAY] was a Phase IIb, randomized, double-blind, multi-national, multi-center, placebo-controlled to evaluate the efficacy of a 3 dose levels of TZESPIRE (280 mg Q2W, 210 mg Q4W, or 70 mg Q4W) in adult subjects with inadequately controlled, severe asthma.

The primary efficacy endpoint was the annualized asthma exacerbation rate (AAER) measured at Week 52. A statistically significant reduction of AAER at Week 52 was observed for all three TZESPIRE dose groups, compared with placebo (AERR of 62%, 71%, and 66% for the 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W TZESPIRE groups, respectively; all $p < 0.001$) in the ITT population.

- ***Study [D5180C00007] ([NAVIGATOR]):***

[NAVIGATOR] was a Phase III, randomized, double-blind, multi-national, multi-center, placebo-controlled to evaluate the efficacy of 210 mg TZESPIRE SC Q4W as add-on maintenance therapy for severe, uncontrolled asthma.

Study [NAVIGATOR] met its primary and key secondary objectives, that is, treatment with 210 mg TZESPIRE SC Q4W demonstrated statistically significant improvement over placebo for all primary and key secondary endpoints during a 52-week study period (Table 6.5-1).

Table 6.5-1 Summary of primary and key secondary efficacy endpoints (FAS)

Variable	Type of estimate	TZESPIRE 210 mg (N = 528)	Placebo (N = 531)	Comparison between groups (95% CI)	99% CI	Unadjusted p-value	Reject H0
Primary efficacy endpoint:							
AAER over 52 weeks (all subjects)	Rate Ratio	528	531	0.44 (0.37, 0.53)	(0.34, 0.57)	< 0.001	Yes
AAER over 52 weeks (subjects with baseline eosinophils < 300 cells/μL)	Rate Ratio	309	309	0.59 (0.46, 0.75)		< 0.001	Yes
Key secondary endpoints							
Pre-BD FEV_1 change from baseline at Week 52	Difference in LSMeans	471	453	0.13 (0.08, 0.18)		< 0.001	Yes
AQLQ(S)+12 Total Score – Change from baseline at Week 52	Difference in LSMeans	480	467	0.33 (0.20, 0.47)		< 0.001	Yes

ACQ-6 Score – Change from baseline at Week 52	Difference in LSMeans	485	472	-0.33 (-0.46, -0.2)		< 0.001	Yes
Change from baseline in weekly mean asthma symptom diary score at Week 52	Difference in LSMeans	374	355	-0.11 (-0.19, -0.04)		0.004	Yes

- ***Study [D5180C00009] ([SOURCE]):***

[SOURCE] was a Phase III, randomized, double-blind, multi-national, multi-center, placebo-controlled study of 210 mg TZESPIRE SC Q4W in subjects with severe asthma. The primary endpoint in this study was not met. For the primary endpoint, the odds of reaching a category of greater percent OCS reduction were numerically higher with TZESPIRE versus placebo, with a cumulative odds ratio (OR) of 1.28 (95% CI: 0.69, 2.35; p = 0.434), but this was not statistically significant.

In summary, results from two pivotal studies ([PATHWAY] and [NAVIGATOR]) have provided sufficient evidence to support the efficacy of 210 mg TZESPIRE SC Q4W as an add-on maintenance treatment in patients with severe asthma aged 12 years and older.

2.4.2 Safety Results

The safety results included the pooled data containing the two 52-week trials, PATHWAY and NAVIGATOR, the OCS-reduction trial, SOURCE, and the extension trial DESTINATION.

Study PATHWAY and NAVIGATOR

A total of 1334 subjects received study treatment, including 665 subjects in the tezepelumab 210 mg Q4W group and 669 subjects in the placebo group.

Overall, the proportions of subjects with any adverse event (AE), serious AE (SAE) or AE leading to treatment discontinuation were similar between the two groups or lower in the tezepelumab 210 mg Q4W group comparing to the placebo group.

The most common AEs in the tezepelumab 210 mg Q4W group were nasopharyngitis, upper respiratory trac infection, headache, and asthma. The incidences of most AEs were generally similar between treatment groups, except for upper respiratory tract infection, asthma, and sinusitis, which were reported with lower incidences in the tezepelumab 210 mg Q4W group compared with the placebo group.

There was no fatal AE in the tezepelumab 210 mg Q4W group.

The most common SAE in both treatment groups was asthma, reported by 15 (2.3%) subjects in the tezepelumab 210 mg Q4W group and 46 (6.9%) subjects in the placebo group. Apart from the SAE of asthma, no other SAE was reported in > 2 subjects in the tezepelumab 210

mg Q4W group.

Eighty-two adolescent subjects were enrolled and received study treatment in trial NAVIGATOR. Tezepelumab 210 mg Q4W was tolerated in adolescent subjects with the AE profile that appeared similar to that seen in adult subjects.

Study SOURCE

A total of 150 subjects received study treatment, including 74 subjects in the tezepelumab 210 mg Q4W group and 76 subjects in the placebo group.

Overall, the proportions of subjects with any AE, SAE or AE leading to treatment discontinuation were similar between the two groups or lower in the tezepelumab 210 mg Q4W group comparing to the placebo group.

The most common AEs in the tezepelumab 210 mg Q4W group were nasopharyngitis, upper respiratory tract infection, asthma, bronchitis bacterial, bronchitis and oral candidiasis. The incidences of most AEs were generally similar between treatment groups.

One subject treated with tezepelumab 210 mg Q4W experienced a fatal AE of cardiac arrest in this study. This subject had past medical history of heart disease. This fatal AE was considered as unrelated to study treatment by the investigator.

The most common SAE in both treatment groups was asthma, reported by 2 (2.7%) subjects in the tezepelumab 210 mg Q4W group and 8 (10.5%) subjects in the placebo group. Apart from the SAE of asthma, no other SAE was reported in > 1 subjects in the tezepelumab 210 mg Q4W group.

Study DESTINAION

The primary objective of this study is to assess the long-term safety of tezepelumab 210 mg Q4W for a total of 104 weeks (with the first year of treatment coming from the predecessor trials, NAVGATOR and SOURCE). There was a slightly higher incidence of Cardiac disorder SOC SAE in the tezepelumab 210 mg Q4W group. The incidence of these events was low and it was hard to draw conclusion based on limited data. Long-term follow-up in order to collect more safety information is necessary.

2.5 Bridging Study Evaluation

Based on population PK analysis, after 210 mg SC Q4W dosing, the mean $C_{max,ss}$ and AUC_{ss} of tezepelumab are 44.5 μg/mL and 970 μg*day/mL in Asian race (N=146), 39.9 μg/mL and 883 μg*day/mL in White race (N=332), respectively. The mean $C_{max,ss}$ and AUC_{ss} of Asian race are 1.12- and 1.10-fold higher than White race, respectively.

Moreover, the mean $C_{max,ss}$ in Japanese (N=58) and Non-Japanese (N=468) following 210 mg SC Q4W dosing are 46.3 and 40.2 μg/mL, respectively. The mean AUC_{ss} in Japanese and Non-Japanese are 1010 and 887 μg*day/mL, respectively. The mean values of both $C_{max,ss}$ and AUC_{ss} are 1.16- and 1.14-fold higher in Japanese compared to Non-Japanese. In addition, the mean C_{min} of 52^{th} weeks are similar in subjects from Taiwan (16.14 μg/mL, N=4) and non-Asian region (19.02 μg/mL, N=334). No significant difference of ethnicity is observed between Asian and non-Asian subjects.

Moreover, the PK of tezepelumab following SC administration of 2.1 to 420 mg and intravenous administration of 210 to 700 mg is linear across this dose range. It's not a steep effect-concentration curve for both efficacy and safety in the range of the recommended dosage and dose regimen. The therapeutic dose range for tezepelumab is not considered to be narrow. Tezepelumab is not a prodrug and it's not metabolized by hepatic enzymes. Overall, race is not considered a sensitive factor on tezepelumab PK.

No clinical specific difference regarding to efficacy and safety was identified based on Asian subgroup analyses (n = 252, 23.8%) from the pivotal Study NAVIGATOR.

2.6 Conclusion

Based on the above multidiscipline review, CDE review team leader recommends approval of tezepelumab.

1. Recommended indication: "as an add-on maintenance treatment in patients with severe asthma aged 12 years and older."
   Limitation: no indicated for the relief of acute bronchospasm or status asthmaticus.
2. Recommended dose: 210 mg by subcutaneous injection every 4 weeks.

3. Post-Marketing Requirements

Submit the clinical study report (CSR) of the following trials once available:

1. Trial D5180C00024 (SUNRISE)
2. Trial D5180C00021 (DIRECTION)
3. EMA Risk Management Plan requirement: Serious cardiac event post-authorization safety study