1. NAME OF THE MEDICINAL PRODUCT

Tezspire 210 mg solution for injection in pre-filled syringe
Tezspire 210 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pre-filled syringe
Each pre-filled syringe contains 210 mg tezepelumab in 1.91 mL solution (110 mg/mL).

Pre-filled pen
Each pre-filled pen contains 210 mg tezepelumab in 1.91 mL (110 mg/mL).

Tezepelumab is a human monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe (injection)
Solution for injection in pre-filled pen (injection)

Clear to opalescent, colourless to light yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TEZSPIRE is indicated for the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma.

4.2 Posology and method of administration

Treatment should be initiated by physicians experienced in the diagnosis and treatment of severe asthma.

Posology

Adults and adolescents (aged 12 years and older)
The recommended dose is 210 mg of tezepelumab by subcutaneous injection every 4 weeks.

Missed dose
If a dose is missed, the dose should be administered as soon as possible. Thereafter, the patient can resume dosing on the scheduled day of administration. If the next dose is already due, then administer as planned. A double dose must not be administered.

Special populations

Elderly (≥65 years of age)
No dose adjustment is required for elderly patients (see section 5.2).

Renal and hepatic impairment
No dose adjustment is required for patients with renal or hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of Tezspire in children under 12 years of age have not been established. No data are available.

Method of administration

Tezspire is administered as a subcutaneous injection.

A patient may self-inject or the patient's caregiver may administer this medicinal product after training in subcutaneous injection technique. Proper training should be provided to patients and/or caregivers on the preparation and administration of Tezspire prior to use according to the "Instructions for Use".

Tezspire should be injected into the thigh or abdomen, except for the 5 cm around the navel. If a healthcare professional or caregiver administers the injection, the upper arm can also be used. A patient should not self-inject in the arm. It should not be injected into areas where the skin is tender, bruised, erythematous, or hardened. It is recommended to rotate the injection site with each injection.

Comprehensive instructions for administration using the pre-filled syringe or pre-filled pen is provided in the "Instructions for Use".

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Acute asthma exacerbations

Tezspire should not be used to treat acute asthma exacerbations.

Asthma-related symptoms or exacerbations may occur during treatment. Patients should be instructed to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment.

Corticosteroids

Abrupt discontinuation of corticosteroids after initiation of therapy is not recommended. Reduction in corticosteroid doses, if appropriate, should be gradual and performed under the supervision of a physician.

Hypersensitivity reactions

Hypersensitivity reactions (e.g. anaphylaxis, rash) may occur following administration of tezepelumab (see section 4.8). These reactions may occur within hours of administration, but in some instances have a delayed onset (i.e. days).

A history of anaphylaxis unrelated to tezepelumab may be a risk factor for anaphylaxis following Tezspire administration. In line with clinical practice, patients should be monitored for an appropriate time after administration of Tezspire.

In the event of a serious hypersensitivity reaction (e.g. anaphylaxis), administration of tezepelumab should be discontinued immediately and appropriate treatment as clinically indicated should be initiated.

Serious infections

Blocking thymic stromal lymphopoietin (TSLP) may theoretically increase the risk of serious infections. In placebo-controlled studies, no increase in serious infections was observed with tezepelumab.

Patients with pre-existing serious infections should be treated before initiating therapy with tezepelumab. If patients develop a serious infection while receiving tezepelumab treatment, therapy with tezepelumab should be discontinued until the serious infection resolves.

Serious cardiac events

In a long-term clinical study, a numerical imbalance in serious cardiac adverse events was observed in patients treated with tezepelumab compared to placebo. No causal relationship between tezepelumab and these events has been established, nor has a patient population at risk of these events been identified.

Patients should be advised of signs or symptoms suggestive of a cardiac event (for example, chest pain, dyspnoea, malaise, feeling lightheaded or faint) and to seek immediate medical attention if such symptoms occur. If patients develop a serious cardiac event while receiving tezepelumab treatment, therapy with tezepelumab should be discontinued until the acute event stabilises.

There is currently no data on re-treatment of patients who develop a serious cardiac event or serious infection.

Parasitic (helminth) infection

TSLP may be involved in the immunological response to some helminth infections. Patients with known helminth infections were excluded from participation in clinical trials. It is unknown if tezepelumab may influence a patient's response against helminth infections.

Patients with pre-existing helminth infections should be treated before initiating therapy with tezepelumab. If patients become infected while receiving treatment and do not respond to anti-helminth treatment, therapy with tezepelumab should be discontinued until infection resolves.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per 210 mg dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

The use of live attenuated vaccines should be avoided in patients receiving tezepelumab.

A clinically relevant effect of tezepelumab on the pharmacokinetics of co-administered asthma medicinal products is not expected. Based on the population pharmacokinetic analysis, commonly co-administered asthma medicinal products (including leukotriene receptor antagonists, theophylline/aminophylline and oral corticosteroids) had no effect on tezepelumab clearance.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of tezepelumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Human IgG antibodies, such as tezepelumab, are transported across the placenta barrier; therefore, Tezspire may be transmitted from the mother to the developing foetus.

As a precautionary measure, it is preferable to avoid the use of Tezspire during pregnancy unless the expected benefit to the pregnant mother is greater than any possible risk to the foetus.

Breast-feeding

It is unknown whether tezepelumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which decreases to low concentrations soon afterwards; consequently, a risk to the breast-fed child cannot be excluded during this short period.

For this specific period, a decision should be made whether to discontinue/abstain from tezepelumab therapy, taking into account the benefit of breast-feeding to the child and the benefit of therapy to the woman.

Afterwards, tezepelumab could be used during breast-feeding if clinically needed.

See section 5.3 for information on the excretion of tezepelumab in animal (cynomolgus monkey) milk.

Fertility

There are no fertility data in humans. Animal studies showed no adverse effects of tezepelumab treatment on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Tezspire has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions during treatment are arthralgia (3.8%) and pharyngitis (4.1%).

Tabulated list of adverse reactions

In clinical studies in patients with severe asthma, a total of 665 patients received at least one dose of Tezspire in trials of 52 weeks duration.

The frequency of adverse reactions is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 List of adverse reactions

System organ class	Adverse reactions	Frequency
Infections and infestations	Pharyngitis[a]	Common
Skin and subcutaneous tissue disorders	Rash[b]	Common
Musculoskeletal and connective tissue disorders	Arthralgia	Common
General disorders and administration site conditions	Injection site reaction[c]	Common

[a] Pharyngitis was defined by the following grouped preferred terms: pharyngitis, pharyngitis bacterial, pharyngitis streptococcal and viral pharyngitis.
[b] Rash was defined by the following grouped preferred terms: rash, rash pruritic, rash erythematous, rash maculo-papular, rash macular.
[c] See 'Description of selected adverse reactions'.

Description of selected adverse reactions

Injection site reactions
In the pooled safety data from PATHWAY and NAVIGATOR, injection site reactions (e.g. injection site erythema, injection site swelling, injection site pain) occurred at a rate of 3.8% in patients treated with tezepelumab 210 mg subcutaneous every 4 weeks (Q4W).

Paediatric population

A total of 82 adolescents aged 12 to 17 with severe, uncontrolled asthma were enrolled in the 52 week Phase 3 NAVIGATOR study (see section 5.1). The safety profile in adolescents was generally similar to the overall study population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose

In clinical trials, doses of up to 280 mg were administered subcutaneously every 2 weeks (Q2W) and doses of up to 700 mg were administered intravenously every 4 weeks (Q4W) to patients with asthma without evidence of dose-related toxicities.

There is no specific treatment for an overdose with tezepelumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, other systemic drugs for obstructive airway diseases, ATC code: R03DX11

Mechanism of action

Tezepelumab is a monoclonal antibody (IgG2λ) directed against thymic stromal lymphopoietin (TSLP), preventing its interaction with the heterodimeric TSLP receptor. In asthma, both allergic and non-allergic triggers induce TSLP production. Blocking TSLP with tezepelumab reduces a broad spectrum of biomarkers and cytokines associated with airway inflammation (e.g. blood eosinophils, airway submucosal eosinophils, IgE, FeNO, IL-5, and IL-13); however, the mechanism of action of tezepelumab in asthma has not been definitively established.

Pharmacodynamic effects

Effect on blood eosinophils and inflammatory biomarkers and cytokines
In clinical trials, administration of tezepelumab 210 mg subcutaneously every 4 weeks reduced blood eosinophils counts, FeNO, IL-5 concentration, IL-13 concentration and serum IgE concentration from baseline compared with placebo. These markers were near maximal suppression after 2 weeks of treatment, except for IgE which declined more slowly. These effects were sustained throughout treatment.

Effect on eosinophils in the airway submucosa
In a clinical trial, administration of tezepelumab 210 mg subcutaneously every 4 weeks reduced submucosal eosinophil counts by 89% compared with a 25% reduction with placebo. Reduction was consistent regardless of baseline inflammatory biomarkers.

Immunogenicity

In NAVIGATOR, anti-drug antibodies (ADA) were detected at any time in 26 (4.9%) out of 527 patients who received tezepelumab at the recommended dosing regimen during the 52-week study period. Of these 26 patients, 10 patients (1.9% of patients treated with tezepelumab) developed treatment-emergent ADA and 1 patient (0.2% of patients treated with tezepelumab) developed neutralising antibodies. ADA titres were generally low and often transient. No evidence of ADA impact on pharmacokinetics, pharmacodynamics, efficacy, or safety was observed.

Clinical efficacy

The efficacy of tezepelumab was evaluated in two randomised, double-blind, parallel group, placebo-controlled clinical trials (PATHWAY and NAVIGATOR) of 52 weeks in duration involving a total of 1609 patients aged 12 years and older with severe asthma. In both trials, patients were enrolled without requiring a minimum baseline level of blood eosinophils or other inflammatory biomarkers (e.g. FeNO or IgE).

PATHWAY was a 52-week exacerbation trial which enrolled 550 patients (18 years of age and older) with severe, uncontrolled asthma to receive treatment with tezepelumab 70 mg subcutaneous Q4W, tezepelumab 210 mg subcutaneous Q4W, tezepelumab 280 mg subcutaneous Q2W or placebo. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment or 1 asthma exacerbation resulting in hospitalisation in the past 12 months.

NAVIGATOR was a 52-week exacerbation trial which enrolled a total of 1061 patients (adults and adolescents 12 years of age and older) with severe, uncontrolled asthma to receive treatment with tezepelumab 210 mg subcutaneous Q4W or placebo. Patients were required to have a history of 2 or

more asthma exacerbations requiring oral or systemic corticosteroid treatment or resulting in hospitalisation in the past 12 months.

In both PATHWAY and NAVIGATOR, patients were required to have an Asthma Control Questionnaire 6 (ACQ-6) score of 1.5 or more at screening, and reduced lung function at baseline (pre-bronchodilator FEV_1 below 80% predicted in adults, and below 90% predicted in adolescents). Patients were required to have been on regular treatment with medium- or high-dose inhaled corticosteroids (ICS) and at least one additional asthma control therapy with or without oral corticosteroids (OCS). High ICS dose was defined as > 500 mcg fluticasone propionate or equivalent per day. Medium ICS dose was defined as > 250 to 500 mcg fluticasone propionate or equivalent per day in PATHWAY and as 500 mcg fluticasone propionate or equivalent per day in NAVIGATOR. Patients continued background asthma therapy throughout the duration of the trials.

The demographics and baseline characteristics of these two trials are provided in **Table 2** below.

Table 2 Demographics and baseline characteristics of asthma trials

	PATHWAY N=550	**NAVIGATOR N=1059**
Mean age (year) (SD)	52 (12)	50 (16)
Female (%)	66	64
White (%)	92	62
Black or African American (%)	3	6
Asian (%)	3	28
Hispanic or Latino (%)	1	15
Mean duration of asthma, (years) (SD)	17 (12)	22 (16)
Never smoked (%)	81	80
High-dose ICS use (%)	49	75
OCS use (%)	9	9
Mean number of exacerbations in previous year (SD)	2.4 (1.2)	2.8 (1.4)
Mean baseline % predicted FEV_1 (SD)	60 (13)	63 (18)
Mean pre-bronchodilator FEV_1 (L) (SD)	1.9 (0.6)	1.8 (0.7)
Mean post-bronchodilator FEV_1 reversibility (%) (SD)	23 (20)	15 (15)
Mean baseline blood EOS count (cells/µL) (SD)	371 (353)	340 (403)
Blood EOS count ≥ 150 cells/µL (%)	76	74
Positive allergic status (%)[a]	46	64
Mean FeNO (ppb) (SD)	35 (39)	44 (41)
FeNO ≥ 25 ppb (%)	44	59
Mean ACQ-6 (SD)	2.7 (0.8)	2.8 (0.8)
Blood EOS count ≥ 150 cells/µL and FeNO ≥ 25 ppb (%)	38	47

[a] Positive allergic status as defined by a positive serum IgE result specific to any perennial aeroallergen in the FEIA panel.
ACQ-6, Asthma Control Questionnaire 6; EOS, Eosinophils; FEIA, Fluorescent enzyme immunoassay; FeNO, Fractional exhaled nitric oxide; FEV_1, Forced expiratory volume in one second; ICS, Inhaled corticosteroid; IgE, Immunoglobulin E; OCS, Oral corticosteroid; ppb, Parts per billion; SD, Standard deviation.

The results summarised below are for the recommended tezepelumab 210 mg subcutaneous Q4W dosing regimen.

Exacerbations

The primary endpoint for PATHWAY and NAVIGATOR was the rate of severe asthma exacerbations measured over 52 weeks. Severe asthma exacerbations were defined as worsening of asthma requiring the use of or increase in oral or systemic corticosteroids for at least 3 days or a single depo-injection of corticosteroids, and/or emergency department visits requiring use of oral or systemic corticosteroids and/or hospitalisation.

In both PATHWAY and NAVIGATOR, patients receiving tezepelumab had significant reductions in the annualised rate of severe asthma exacerbations compared with placebo (**Table 3** and **Table 4**). There were also fewer exacerbations requiring emergency room visits and/or hospitalisation in patients treated with tezepelumab compared with placebo. In PATHWAY and NAVIGATOR, severe asthma exacerbations requiring emergency room visits and/or hospitalisation were reduced by 85% and 79% with tezepelumab 210 mg subcutaneous Q4W, respectively.

Table 3 Rate of severe exacerbations at week 52 in NAVIGATOR[a]

	Tezepelumab (N=528)	**Placebo (N=531)**
Annualised severe asthma exacerbation rate		
Rate	0.93	2.10
Rate ratio (95% CI)	0.44 (0.37, 0.53)	
p-value	<0.001	

[a] Time at risk is defined as the total duration of time in which a new exacerbation can occur (i.e. total follow-up time minus time during exacerbation and 7 days after).
CI, Confidence interval

Table 4 Rate of severe exacerbations at week 52 in PATHWAY[a]

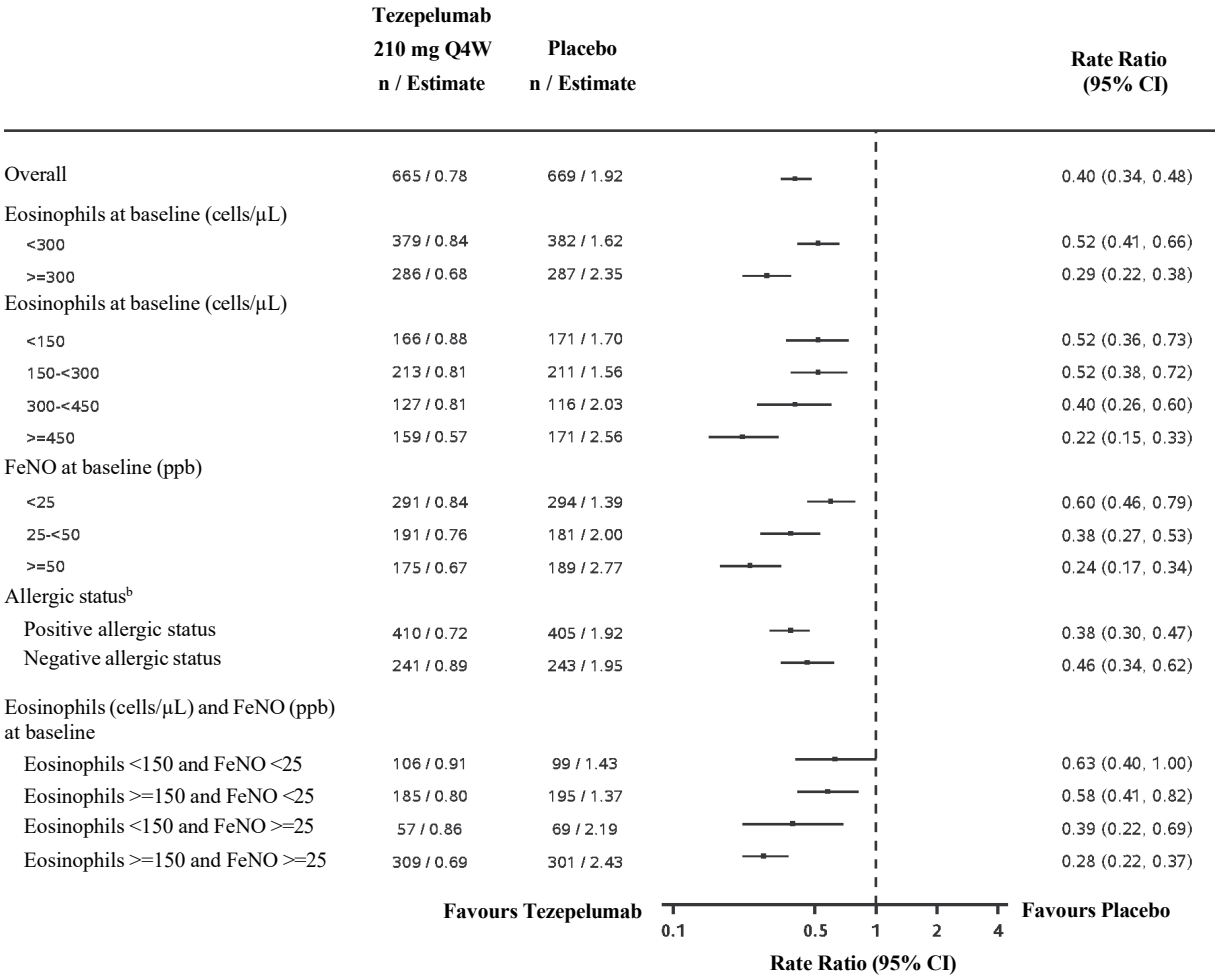
	Tezepelumab (N=137)	**Placebo (N=138)**
Annualised severe asthma exacerbation rate		
Rate	0.20	0.72
Rate ratio (95% CI)	0.29 (0.16, 0.51)	
p-value	<0.001	

[a] Time at risk is defined as the total follow-up time.
CI, Confidence interval

Subgroup analysis
In NAVIGATOR, tezepelumab demonstrated a reduction in the rate of severe asthma exacerbations regardless of the baseline levels of blood eosinophils, FeNO, as well as allergic status (determined by a perennial aeroallergen specific IgE). Similar results were seen in PATHWAY. See **Figure 1**.

In NAVIGATOR, reductions in the rate of severe asthma exacerbations were greater with increasing baseline blood eosinophil counts and FeNO values (rate ratio = 0.79 [95% CI: 0.48, 1.28] for patients with both baseline blood eosinophil count < 150 cells/µL and baseline FeNO < 25 ppb; rate ratio = 0.30 [95% CI: 0.23, 0.40] for patients with both baseline blood eosinophil count ≥ 150 cells/µL and baseline FeNO ≥ 25 ppb).

Figure 1 Annualised asthma exacerbation rate ratio over 52 weeks across different baseline biomarkers for the Full Analysis Set (pooled NAVIGATOR and PATHWAY)[a]



[a] Time at risk is defined as the total duration of time in which a new exacerbation can occur (i.e. total follow-up time minus time during exacerbation and 7 days after).

[b] Allergic status as defined by a serum IgE result specific to any perennial aeroallergen in the FEIA panel.

Lung function

Change from baseline in FEV_1 was assessed as a secondary endpoint in NAVIGATOR. Compared with placebo, tezepelumab provided clinically meaningful improvements in the mean change from baseline in FEV_1 **(Table 5)**.

Patient reported outcomes

Changes from baseline in ACQ-6, Standardised Asthma Quality of Life Questionnaire for ages 12 and older [AQLQ(S)+12] and weekly mean Asthma Symptom Diary (ASD) scores were assessed as secondary endpoints in NAVIGATOR. Severity of wheezing, shortness of breath, cough, and chest tightness were assessed twice daily (morning and evening). Night-time awakening and activity were assessed on a daily basis. The total ASD score was calculated as the mean of 10 items **(Table 5)**.

Improvements in ACQ-6 and AQLQ(S)+12 were seen as early as 2 weeks and 4 weeks after administration of tezepelumab, respectively, and sustained through week 52 in both trials.

Table 5 Results of key secondary endpoints at week 52 in NAVIGATOR[a]

	Tezepelumab	Placebo
Pre-bronchodilator FEV_1		
N	527	531
LS Mean Change from Baseline (L)	0.23	0.10
LS Mean Difference from Placebo (L) (95% CI)	0.13 (0.08, 0.18)	
p-value	<0.001	
AQLQ(S)+12 total score		
N	525	526
LS Mean Change from Baseline	1.48	1.14
Difference from Placebo (95% CI)	0.33 (0.20, 0.47)	
p-value	<0.001	
ACQ-6 score		
N	527	531
LS Mean Change from Baseline	-1.53	-1.20
Difference from Placebo (95% CI)	-0.33 (-0.46, -0.20)	
p-value	<0.001	
ASD		
N	525	531
LS Mean Change from Baseline	-0.70	-0.59
Difference from Placebo (95% CI)	-0.11 (-0.19, -0.04)	
p-value	0.004	

[a] Estimates are derived from a Mixed Model for Repeated Measures (MMRM) using all available data from patients with at least 1 change from baseline value, including data post-discontinuation.

ACQ-6, Asthma Control Questionnaire 6; AQLQ(S)+12, Standardised Asthma Quality of Life Questionnaire for 12 years and older; ASD Asthma Symptom Diary; CI, Confidence interval; FEV_1, Forced expiratory volume in one second; LS, Least square; N, Number of patients contributing to the analysis (FA) with at least 1 change from baseline value

Elderly patients (≥ 65 years of age)

Of the 665 patients with asthma exposed to tezepelumab 210 mg subcutaneous Q4W in PATHWAY and NAVIGATOR, a total of 119 patients were 65 years of age or older, of which 32 patients were 75 years of age or older. Safety in these age groups were similar to the overall study population. Efficacy in these age groups were similar to the overall study population in NAVIGATOR. PATHWAY did not include sufficient numbers of patients aged 65 and over to determine efficacy in this age group.

Paediatric population

A total of 82 adolescents aged 12 to 17 with severe, uncontrolled asthma were enrolled in NAVIGATOR and received treatment with tezepelumab (n=41) or placebo (n=41). Of the 41 adolescents receiving treatment with tezepelumab, 15 were taking high-dose ICS at baseline. The annualised asthma exacerbation rate observed in adolescents treated with tezepelumab was 0.68 versus 0.97 for placebo (rate ratio 0.70; 95% CI 0.34, 1.46). The LS mean change from baseline for FEV_1 observed in adolescents treated with tezepelumab was 0.44 L versus 0.27 L for placebo (LS mean

difference 0.17 L; 95% CI -0.01, 0.35). The pharmacodynamic responses in adolescents were generally similar to the overall study population.

5.2 Pharmacokinetic properties

The pharmacokinetics of tezepelumab were dose-proportional following subcutaneous administration over a dose range of 2.1 mg to 420 mg.

Absorption

Following a single subcutaneous administration, the maximum serum concentration was reached in approximately 3 to 10 days. Based on population pharmacokinetic analysis, the estimated absolute bioavailability was approximately 77%. There was no clinically relevant difference in bioavailability when administered to different injection sites (abdomen, thigh, or upper arm).

Distribution

Based on population pharmacokinetic analysis, central and peripheral volume of distribution of tezepelumab were 3.9 L and 2.2 L, respectively, for a 70 kg individual.

Metabolism

Tezepelumab is a human monoclonal antibody (IgG2λ) that is degraded by proteolytic enzymes widely distributed in the body and not metabolised by hepatic enzymes.

Elimination

As a human monoclonal antibody, tezepelumab is eliminated by intracellular catabolism and there is no evidence of target-mediated clearance. From population pharmacokinetic analysis, the estimated clearance for tezepelumab was 0.17 L/d for a 70 kg individual. The elimination half-life was approximately 26 days.

Special populations

Age, gender, race
Based on population pharmacokinetic analysis, age, gender and race had no clinically meaningful effects on the pharmacokinetics of tezepelumab.

Body weight
Based on population pharmacokinetic analysis, higher body weight was associated with lower exposure. However, the effect of body weight on exposure had no meaningful impact on efficacy or safety and does not require dose adjustment.

Paediatric patients
Based on the population pharmacokinetic analysis, there was no clinically meaningful age-related difference in the pharmacokinetics of tezepelumab between adults and adolescents aged 12 to 17 years. Tezepelumab has not been studied in children under 12 years of age (see section 4.2).

Elderly patients (≥65 years of age)
Based on population pharmacokinetic analysis, there was no clinically meaningful difference in the pharmacokinetics of tezepelumab between patients 65 years of age or older and younger patients.

Renal impairment
No formal clinical studies have been conducted to investigate the effect of renal impairment on tezepelumab. Based on population pharmacokinetic analysis, tezepelumab clearance was similar in patients with mild renal impairment (creatinine clearance 60 to < 90 mL/min), moderate renal impairment (creatinine clearance 30 to < 60 mL/min) and those with normal renal function (creatinine clearance ≥ 90 mL/min). Tezepelumab has not been studied in patients with severe renal impairment (creatinine clearance < 30 mL/min); however, tezepelumab is not cleared renally.

Hepatic impairment
No formal clinical studies have been conducted to investigate the effect of hepatic impairment on tezepelumab. IgG monoclonal antibodies are not primarily cleared via hepatic pathway; change in hepatic function is not expected to influence tezepelumab clearance. Based on population pharmacokinetic analysis, baseline hepatic function biomarkers (ALT, AST, and bilirubin) had no effect on tezepelumab clearance.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on repeated dose toxicity studies including safety pharmacology and fertility evaluations, and an ePPND (enhanced Pre- and Post-Natal Development) reproductive toxicity study in cynomolgus monkeys at doses of up to 300 mg/kg/week (producing exposures of greater than 100-times the clinical exposure at maximum recommended human dose [MRHD]).

Tezepelumab is excreted in milk in monkeys, although at low concentrations (< 1%).

Tezepelumab is a monoclonal antibody, as such genotoxicity and carcinogenicity studies have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
L-proline
Acetic acid, glacial
Polysorbate 80
Sodium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.

After removal from refrigeration, may be kept at room temperature (20°C - 25°C) for a maximum of 30 days. Do not put back in the refrigerator once TEZSPIRE has reached room temperature.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). For storage after removal from refrigeration, see section 6.3.
Keep the pre-filled syringe or pre-filled pen in the outer carton in order to protect from light until time of use. Do not freeze. Do not shake. Do not expose to heat.

6.5 Nature and contents of container

Pre-filled syringe

1.91 mL solution in a siliconized Type I glass pre-filled syringe subassembly consisting of a 27-gauge ½-inch (12.7 mm) stainless steel special thin wall needle covered with a rigid needle cover and bromobutyl plunger-stopper. The pre-filled syringe subassembly is assembled with a needle guard and an extended finger flange.

Pack sizes:
Pack containing 1 pre-filled syringe

Pre-filled pen

1.91 mL solution in a siliconized Type I glass pre-filled syringe subassembly consisting of a 27-gauge ½-inch (12.7 mm) stainless steel special thin wall needle covered with a needle cover and plunger-stopper. The pre-filled pen consists of the pre-filled syringe subassembly and handheld, mechanical (spring-based) injection device.

Pack sizes:
Pack containing 1 pre-filled pen.

6.6 Special precautions for disposal and other handling

This medicinal product is for single-use only.

Prior to administration, remove carton from refrigerator and allow Tezspire to reach room temperature. This generally takes 60 minutes.

Visually inspect Tezspire for particulate matter and discolouration prior to administration. Tezspire is clear to opalescent, colourless to light yellow. Do not use this medicinal product if liquid is cloudy, discoloured, or if it contains large particles or foreign particulate matter.

Additional information and instructions for the preparation and administration of Tezspire using the pre-filled syringe or pre-filled pen are given in the package leaflet and 'Instructions for Use'.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Amgen Manufacturing Limited
Puerto Rico
United States

8. MARKETING AUTHORISATION HOLDER

Astrazeneca (Israel) Ltd.,
1 Atirei Yeda St.,
Kfar Saba 4464301.

Revised in May 2023 according to MoH guidelines.