PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

TEZSPIRE™

tezepelumab injection

solution for injection, 110 mg/mL, subcutaneous use

210 mg single-use, pre-filled syringe
210 mg single-use, pre-filled pen

Professed

anti-thymic stromal lymphopoietin, human monoclonal antibody

ATC Code: R03DX11

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RECENT MAJOR LABEL CHANGES

Not Applicable

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TEZSPIRE (tezepelumab injection) is indicated as an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma.

TEZSPIRE is not indicated for relief of acute bronchospasm or status asthmaticus (see 7 WARNINGS AND PRECAUTIONS).

1.1 Pediatrics

Pediatrics (<12 years of age): The safety and efficacy of Tezspire in children <12 years old have not been established.

1.2 Geriatrics

Geriatrics (≥65 years of age): Of the 665 patients with asthma treated with Tezspire in clinical trials (PATHWAY and NAVIGATOR) for severe asthma, 119 patients (18%) were 65 years or older. While the data was limited, no overall differences in safety or efficacy of Tezspire have been observed between patients 65 years of age and older and younger patients. Sensitivity of some older individuals cannot be excluded (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

Tezspire (tezepelumab injection) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Tezspire (tezepelumab injection) is administered as a subcutaneous (SC) injection.

A patient may self-inject Tezspire or the patient's caregiver may administer Tezspire after training in subcutaneous injection technique. Provide proper training to patients and/or caregivers on the preparation and administration of Tezspire prior to use according to the "INSTRUCTIONS FOR USE".

4.2 Recommended Dose and Dosage Adjustment

Adults and adolescents (aged 12 years and older)

The recommended dose is 210 mg of Tezspire by subcutaneous injection every 4 weeks (Q4W).

Pediatrics (<12 years of age): The safety and efficacy of Tezspire in children under 12 years of age have not been established.

Geriatrics (≥65 years of age): No dose adjustment is required for elderly patients age 65 or older based on population-PK modeling (see Special Populations and Conditions).

Renal impairment: No dose adjustment is required for patients with renal impairment based on population-PK modeling (see Special Populations and Conditions).

Hepatic impairment: No dose adjustment is required for patients with hepatic impairment based on population-PK modeling (see Special Populations and Conditions).

4.4 Administration

Tezspire is administered as a subcutaneous injection.

A patient may self-inject Tezspire or the patient's caregiver may administer Tezspire after training in subcutaneous injection technique. Provide proper training 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 (2 inches) 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. Tezspire 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.

Instructions for Preparation and Use

Pre-filled Syringe and Pre-filled Pen
Tezspire is for single use only.

Tezspire solution for subcutaneous injection is supplied in a sterile, pre-filled syringe or sterile, pre-filled pen for individual use. Do not shake. Do not freeze. Protect from light.

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

Tezspire may be kept at room temperature (20°C to 25°C) for a maximum of 30 days. Do not put back in the refrigerator once Tezspire has reached room temperature. After removal from the refrigerator, Tezspire must be used within 30 days or discarded.

Visually inspect Tezspire for particulate matter and discolouration prior to administration. Tezspire is clear to opalescent, colourless to light yellow. Do not use Tezspire 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 relevant "INSTRUCTIONS FOR USE".

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

4.5 Missed Dose

If a dose is missed, administer the dose as soon as possible. Thereafter, the patient can resume dosing on the usual day of administration. If the next dose is already due, then administer as planned.

5 OVERDOSAGE

Tezepelumab doses of up to 280 mg SC every 2 weeks (Q2W) and doses of up to 700 mg intravenously (IV) Q4W have been administered clinically 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1 – Dosage Forms, Strengths and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous use	Solution / 110 mg/mL in a: • 1.91 mL single-use, pre-filled syringe or • 1.91 mL single-use, pre-filled pen	Glacial acetic acid, L-proline, Polysorbate 80, Sodium hydroxide, Water for injection

Dosage Form Description

Tezspire (tezepelumab injection) is a sterile, preservative-free solution intended for subcutaneous injection.

Packaging

Pre-filled syringe
Tezspire is available in a pack containing 1 single-use, sterile, pre-filled syringe. Each single-use, pre-filled syringe contains a solution of 210 mg tezepelumab in 1.91 mL (110 mg/mL) in a pre-filled syringe subassembly consisting of a siliconized Type I glass syringe barrel with a plunger-stopper and a 27-gauge 12.7 mm (½-inch) stainless steel special thin-wall needle covered with a needle cover. The pre-filled syringe subassembly is assembled with a needle guard and an extended finger flange. The needle cover is not made with natural rubber latex.

Pre-filled pen
Tezspire is available in a pack containing 1 single-use, sterile, pre-filled pen. Each single-use, pre-filled pen contains a solution of 210 mg tezepelumab in 1.91 mL (110 mg/mL) in a pre-filled syringe subassembly consisting of a siliconized Type I glass syringe barrel with a plunger-stopper and a 27-gauge 12.7 mm (½-inch) stainless steel special thin-wall needle covered with a needle cover. The pre-filled pen consists of the pre-filled syringe subassembly and handheld, mechanical (spring-based) injection device. The needle cover is not made with natural rubber latex.

7 WARNINGS AND PRECAUTIONS

General

Acute Asthma Symptoms or Deteriorating Disease

Tezspire (tezepelumab injection) should not be used to treat acute symptoms or asthma exacerbations. **Do not use Tezspire to treat acute bronchospasm or status asthmaticus.**

Patients should be instructed to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment.

Reduction of Corticosteroid Dosage

Abrupt discontinuation of corticosteroids after initiation of Tezspire therapy is not recommended. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy. Reduction in corticosteroid doses, if appropriate, should be gradual and performed under the supervision of a physician.

Cardiovascular

Serious Cardiac Events

In a long-term clinical trial, a numerical imbalance in serious cardiac adverse events has been observed in patients treated with Tezspire compared to placebo. All patients who experienced a serious cardiac adverse event had an existing cardiovascular disorder or at least one cardiovascular risk factor at baseline. No causal relationship between Tezspire and these events has been established, nor has a patient population at risk of these events been identified (see 8.2 Clinical Trial Adverse Reactions).

Patients should be advised of signs or symptoms suggestive of a cardiac event (for example, chest pain, dyspnea, malaise, feeling lightheaded or faint) and to seek immediate medical attention if such symptoms occur.

Gastrointestinal

Parasitic (Helminth) Infection

Thymic stromal lymphopoietin (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 Tezspire may influence a patient's response against helminth infections.

Treat patients with pre-existing helminth infections before initiating therapy with Tezspire. If patients become infected while receiving treatment with Tezspire and do not respond to anti-helminth treatment, discontinue treatment with Tezspire until infection resolves.

Immune

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 Tezspire.

Patients with pre-existing serious infections should be treated before initiating therapy with Tezspire. If patients develop a serious infection while receiving Tezspire treatment and do not respond to treatment, therapy with Tezspire should be discontinued until the serious infection resolves.

Reproductive Health: Female and Male Potential

- **Fertility**

  No data are available on the effect of Tezspire on human fertility.

Sensitivity/Resistance

Hypersensitivity reactions: Hypersensitivity reactions (e.g. anaphylaxis, rash) may occur following administration of Tezspire (see 8 ADVERSE REACTIONS). These reactions may occur within hours of administration, but in some instances have a delayed onset (i.e. days).

In the event of a hypersensitivity reaction, appropriate treatment as clinically indicated should be initiated and an individualized decision on whether to continue or discontinue treatment with Tezspire should be made.

7.1 Special Populations

7.1.1 Pregnant Women

No studies have been conducted with Tezspire in pregnant women and relevant data from clinical use are very limited. As a precautionary measure, it is preferable to avoid the use of Tezspire during pregnancy.

Human IgG antibodies, such as tezepelumab, are transported across the placenta barrier; therefore, Tezspire may be transmitted from the mother to the developing fetus. In addition, tezepelumab was detected in monkey infant serum following *in utero* exposure, indicating transport across the placenta (see 16 NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

There is no information regarding the presence of tezepelumab in human milk, the effects of tezepelumab on the breast-fed infant, or the effects of tezepelumab on milk production. However, tezepelumab is a human monoclonal antibody immunoglobulin G2λ (IgG2λ), and immunoglobulin G (IgG) is present in human milk in small amounts. Animal data demonstrated that tezepelumab was present in the milk of cynomolgus monkeys postpartum following dosing during pregnancy (see 16 NON-CLINICAL TOXICOLOGY).

7.1.3 Pediatrics

Pediatrics (< 12 years of age): The safety and efficacy of Tezspire in children <12 years old have not been established.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): Of the 665 patients with asthma treated with Tezspire in clinical trials (PATHWAY and NAVIGATOR) for severe asthma, 119 patients (18%) were 65 years or older. While the data was limited, no overall differences in safety or efficacy of Tezspire have been observed between patients 65 years of age and older and younger patients. Sensitivity of some older individuals cannot be excluded.

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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In clinical studies in patients with severe asthma, the most commonly reported adverse

reactions during treatment were arthralgia and pharyngitis.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of Tezspire was based on the pooled safety population from PATHWAY and NAVIGATOR, which consists of 665 adult and pediatric patients 12 years of age and older with severe asthma who received at least one dose of Tezspire 210 mg subcutaneously once every 4 weeks. The two placebo-controlled clinical trials were of 52 weeks duration. In addition, a similar safety profile was seen in a trial that enrolled 150 adult patients with severe asthma who required treatment with daily oral corticosteroids (i.e. SOURCE).

Adverse reactions that occurred at an incidence greater than or equal to 1% and more common than in the placebo group from the pooled safety population are shown in Table 2.

Table 2 Adverse Reactions with Tezspire with Incidence Greater than or Equal to 1% and More Common than Placebo in Patients with Severe Asthma (PATHWAY and NAVIGATOR)

Adverse Reaction	Tezspire N=665 n (%)	Placebo N=669 n (%)
General disorders and administration site conditions		
Injection site reaction	25 (3.8)	21 (3.1)
Infections and infestations		
Pharyngitis*	27 (4.1)	18 (2.7)
Musculoskeletal and connective tissue disorders		
Arthralgia	25 (3.8)	16 (2.4)
Skin and subcutaneous tissue disorders		
Rash†	10 (1.5)	8 (1.2)
Nervous system disorders		
Headache	9 (1.4)	5 (0.7)

* Pharyngitis (including Pharyngitis, Pharyngitis bacterial, Pharyngitis streptococcal and Viral pharyngitis)

† Rash (including Rash, Rash pruritic, Rash erythematous, Rash maculo-papular, Rash macular)

Injection site reactions

In the pooled safety population, 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 SC Q4W compared with 3.1% in patients treated with placebo.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to tezepelumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

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 antibodies and 1 patient (0.2% of patients treated with tezepelumab) developed neutralizing antibodies. ADA titres were generally low and often transient. The presence of ADAs had no clinically meaningful impact on tezepelumab pharmacokinetics, pharmacodynamics, efficacy, or safety.

Serious cardiac events

In a long-term extension trial in patients with severe asthma, 839 patients from NAVIGATOR and SOURCE were treated with Tezspire 210 mg SC Q4W for up to 104 weeks. A numerical imbalance in cardiac disorder SOC SAEs was observed with more events in patients treated with Tezspire vs placebo (exposure-adjusted incidence rates per 100 patient years were 1.30 [95% CI: 0.77, 2.06] versus 0.23 [95% CI: 0.03, 0.83] respectively). The rate of adjudicated major adverse cardiovascular events (MACE) observed were 0.65 for Tezspire (per 100 patient years) vs 0.46 for placebo (per 100 patient years) with an incidence rate difference per 100 patient years of 0.19 (95% CI: -0.58, 0.85). Serious cardiac events were varied (eg, cardiac arrhythmias, coronary artery disease, heart failures, and myocardial disorders) with no apparent pattern. No causal relationship between Tezspire and these events has been established, nor were these imbalances seen in other Tezspire trials. The safety profile during the long-term extension trial was generally similar to the known safety profile of Tezspire.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

The safety profile in adolescents with severe, uncontrolled asthma over 52 weeks in NAVIGATOR (n=82) was generally similar to the overall study population.

8.3 Less Common Clinical Trial Adverse Reactions

Adverse reactions (investigator assessed causality) reported in < 1% of patients on Tezspire 210 mg SC Q4W treatment not previously listed are summarized below:

General Disorders and Administration Site Conditions: Fatigue

9 DRUG INTERACTIONS

9.3 Drug-Behavioural Interactions

Interactions with behaviour have not been established.

9.4 Drug-Drug Interactions

No formal drug interaction studies have been performed.

Based on the population pharmacokinetic analysis, commonly co-administered asthma medications (including leukotriene receptor antagonists, theophylline/aminophylline, and oral corticosteroids (OCS)) had no clinically meaningful effect on tezepelumab clearance.

Drug-Vaccine Interactions

The use of live attenuated vaccines should be avoided in patients receiving Tezspire (tezepelumab injection).

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Tezepelumab is an anti-TSLP, human monoclonal antibody (IgG2λ) that binds to human TSLP. This binding prevents the interaction of TSLP with the heterodimeric TSLP receptor, thereby inhibiting the biological activity of TSLP. TSLP is a cytokine mainly derived from epithelial cells and occupies an upstream position at the top of the asthma inflammatory cascade.

Airway inflammation is an important component in the pathogenesis of asthma. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes, ILC2 cells) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in airway inflammation. Blocking TSLP with tezepelumab reduces a broad spectrum of downstream biomarkers and cytokines associated with inflammation (e.g., blood eosinophils, immunoglobulin E (IgE), fractional exhaled nitric oxide (FeNO), interleukin 5 (IL-5), and interleukin 13 (IL-13)); however, the mechanism of tezepelumab action in asthma has not been definitively established.

10.2 Pharmacodynamics

In a Phase 3 exacerbation trial (NAVIGATOR), administration of tezepelumab 210 mg SC Q4W (n=528) reduced inflammatory biomarkers and cytokines from baseline compared with placebo (n=531) with an onset of effect by 2 weeks and sustained reduction to 52 weeks for blood eosinophil counts, FeNO, serum IL- 5 concentration, and serum IL-13 concentration. Tezepelumab caused a progressive reduction in serum total IgE concentration, with levels continuing to decrease throughout 52 weeks of treatment. Similar effects were seen in PATHWAY.

10.3 Pharmacokinetics

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

Table 3 Pharmacokinetic parameters for tezepelumab

Parameter	$AUC_{0\text{-}4wks,ss}$ (µg*day/mL)[a]	C_{max} (µg/mL)[a]	t_{max} (day)[b]	V_c (L)[c]	V_p (L)[c]	CL (L/day)[c]	$t_{1/2}$ (days)[c]
Mean	901	40.9	3-10	3.9	2.2	0.17	26

[a] Simulated tezepelumab exposures in the Phase 3 study NAVIGATOR. Mean values of the area under the curve ($AUC_{0\text{-}4wks,ss}$) at steady state over 4 weeks and the maximum concentration at steady state (C_{max}) following SC administration of tezepelumab 210 mg Q4W to asthma patients above 12 years with a median body weight of 76 kg.

[b] Time to maximum observed serum concentration, t_{max}, reported as a range of medians from observed data in Phase 1 studies following single SC dose administration

[c] Pharmacokinetic parameters based on population pharmacokinetic analysis for a typical individual of 70 kg (V_c, central volume of distribution, V_p, peripheral volume of distribution, CL, clearance and $t_{1/2}$, elimination half-life)

Absorption: Following a single SC 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 exposure when administered to different injection sites (abdomen, thigh, or upper arm). After repeated SC administration Q4W, serum tezepelumab concentrations approached steady state by 12 weeks.

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 that is degraded by proteolytic enzymes widely distributed in the body and not metabolized 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 and Conditions

Based on population pharmacokinetic analysis, age, gender, race, disease severity, baseline biomarkers, concomitant asthma medications and smoking history had no clinically meaningful effects on the pharmacokinetics of tezepelumab.

- **Adolescents (≥12 years of age):** Based on 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 4.2 Recommended Dose and Dosage Adjustment).
- **Geriatrics (≥65 years of age):** Based on population pharmacokinetic analysis on a limited number of patients (n = 119 [18%]), there was no clinically meaningful difference in the pharmacokinetics of tezepelumab between patients 65 years of age or older and younger patients.
- **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. Body

Mass Index also had no meaningful impact on efficacy or safety and does not require dose adjustment.

- **Hepatic Insufficiency:** No formal clinical studies have been conducted to investigate the effect of hepatic impairment on tezepelumab. Based on population pharmacokinetic analysis, baseline hepatic function biomarkers (ALT, AST, and bilirubin) had no effect on tezepelumab clearance.
- **Renal Insufficiency:** 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) or in patients with end stage renal disease.

11 STORAGE, STABILITY AND DISPOSAL

Store in a refrigerator (2°C to 8°C). Store the pre-filled syringe and pre-filled pen in the original package in order to protect from light.

Do not freeze. Do not shake. Do not expose to heat.

For storage conditions after removal from the refrigerator, see 4.4 Administration.

For disposal, see 4.4 Administration.

12 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: tezepelumab

Chemical name: Anti-thymic stromal lymphopoietin monoclonal antibody

Molecular formula and molecular mass: Tezepelumab is comprised of two heavy chains and two light chains with an overall molecular weight of approximately 147 kDa.

Structural formula: Tezepelumab is a human monoclonal antibody of the immunoglobulin G2 (IgG2) subclass consisting of 2 heavy chains and 2 light chains of the lambda subclass. Tezepelumab contains a total of 36 cysteine residues involved in both intrachain and interchain disulfide bonds. Each heavy chain contains 448 amino acids with 4 intrachain disulfides. Each light chain contains 214 amino acids with 2 intrachain disulfides. Each heavy chain contains an N-linked glycan at a consensus glycosylation site on asparagine 298.

Physicochemical properties: Tezepelumab has an isoelectric point (pI) of 7.2 and an extinction coefficient (determined experimentally) of 1.7 $(mg/mL)^{-1}cm^{-1}$.

Pharmaceutical standard: Professed

Product Characteristics:

Tezepelumab is a human monoclonal immunoglobulin that specifically binds to human thymic stromal lymphopoietin and prevents its interaction with the TSLP receptor.

The drug product is supplied as a sterile, preservative-free solution that is clear to opalescent and colorless to light yellow, intended for subcutaneous injection. Each single-use, pre-filled syringe or pre-filled pen contains 210 mg drug product in 1.91 mL deliverable volume.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Severe Asthma

Table 4 Summary of patient demographics for clinical trials in asthma

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
D5180C00007 (NAVIGATOR)	Phase 3, randomized, double-blind, placebo controlled, exacerbation trial to evaluate the efficacy and safety of tezepelumab in adults and adolescents with severe uncontrolled asthma	Tezspire 210 mg Q4W SC or placebo 52-week treatment period with 12-week safety follow-up for subjects not rolling over to long-term extension	1061* randomized 210 mg SC Q4W: 529 Placebo SC Q4W: 532	50 (12-80)	64% Female
CD-RI-MEDI9929-1146 (PATHWAY)	Phase 2 randomized, double-blind, placebo-controlled exacerbation trial to evaluate the efficacy and safety of tezepelumab	Tezspire SC 70 mg Q4W, 210 mg Q4W, 280 mg Q2W SC or placebo 52-week treatment period with 12-week safety follow-up	550 randomized 280 mg SC Q2W: 137 210 mg SC Q4W: 137 70 mg SC Q4W: 138 Placebo SC Q2W: 138	52 (20-75)	66% Female

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
	in adult subjects with severe, uncontrolled asthma				

Q2W: every 2 weeks; Q4W: every 4 weeks; SC: subcutaneous

* 1059 patients received at least one dose

The efficacy of Tezspire (tezepelumab injection) was evaluated in two randomized, double-blind, parallel group, placebo-controlled clinical trials (Study CD-RI-MEDI9929-1146 (PATHWAY) and Study D5180C00007 (NAVIGATOR) of 52 weeks in duration in patients aged 12 years and older. In PATHWAY, subjects were required to have a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment or 1 asthma exacerbation resulting in hospitalization in the past 12 months. In NAVIGATOR, patients were required to have a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment or resulting in hospitalization 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 FEV1 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 controller with or without OCS. The 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. In both trials, patients were enrolled without requiring a minimum baseline level of blood eosinophils or other inflammatory biomarkers (e.g. FeNO or IgE). Patients continued background asthma therapy throughout the duration of the trials.

The demographics and baseline characteristics of these two trials are provided in in Table 5 below.

Table 5 Demographics and Baseline Characteristics of Asthma Trials

	NAVIGATOR N=1059	PATHWAY N=550
White (%)	62	92
Asian (%)	28	3
Never smoked (%)	80	81
High-dose ICS use (%)	75	49
OCS use (%)	9	9
Mean number of exacerbations in previous year (SD)	2.8 (1.4)	2.4 (1.2)
Mean duration of asthma (years) (SD)	22 (16)	17 (12)
Mean baseline % predicted FEV1 (SD)	63 (18)	60 (13)
Mean post-bronchodilator FEV1 reversibility (%) (SD)	15 (15)	23 (20)
Mean baseline blood EOS count (cells/µL) (SD)	340 (403)	371 (353)
Positive allergic status (%)*	64	46
Mean FeNO (ppb) (SD)	44 (41)	35 (39)
Mean ACQ-6 (SD)	2.8 (0.8)	2.7 (0.8)

* 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; FEV1, Forced expiratory volume in one second; ICS, Inhaled corticosteroid; IgE, Immunoglobulin E; OCS, Oral corticosteroid; ppb, Parts per billion; SD, Standard deviation.

Study Results

The primary endpoint for PATHWAY (results for 210 mg SC Q4W dosing reflected below) and NAVIGATOR was the rate of clinically significant asthma exacerbations measured over 52 weeks. Clinically significant 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 hospitalization. Key secondary endpoints for NAVIGATOR were the change from baseline in pre-dose pre-bronchodilator FEV_1, change from baseline in Standardised Asthma Quality of Life Questionnaire for ages 12 and older (AQLQ(S)+12) total score and change from baseline in Asthma Control Questionnaire 6 (ACQ-6) score at 52 weeks.

Exacerbations

In both PATHWAY and NAVIGATOR, patients receiving Tezspire had statistically significant and clinically meaningful reductions in the annualized rate of asthma exacerbations compared with placebo (Table 6).

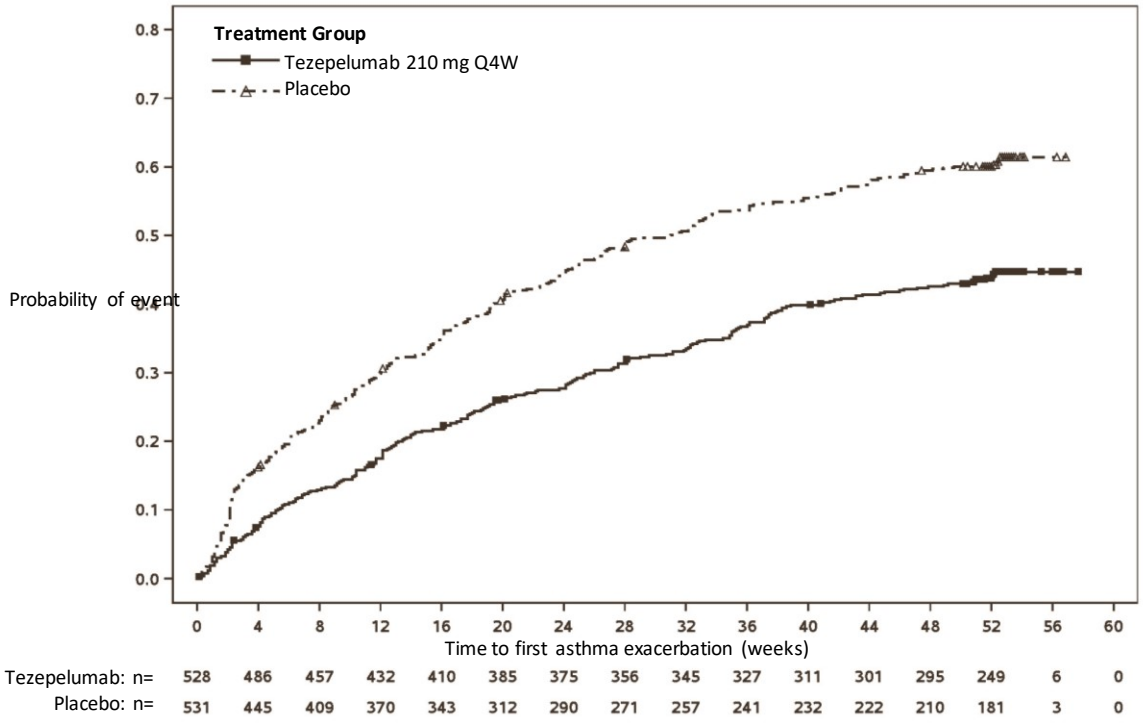
Table 6 Rate of Clinically Significant Exacerbations Over 52 Weeks, NAVIGATOR and PATHWAY

Trial	Treatment	Exacerbations per year	
		Rate***	Rate Ratio (95% CI)
Annualized Asthma Exacerbation Rate			
NAVIGATOR	Tezspire (N=528)	0.93	0.44 (0.37, 0.53)
	Placebo (N=531)	2.10	
PATHWAY	Tezspire (N=137)	0.20	0.29 (0.16, 0.51)
	Placebo (N=138)	0.72	
Exacerbations requiring emergency room visit/hospitalization			
NAVIGATOR	Tezspire (N=528)	0.06	0.21 (0.12, 0.37)
	Placebo (N=531)	0.28	
PATHWAY	Tezspire (N=137)	0.03	0.15 (0.04, 0.58)
	Placebo (N=138)	0.18	

*** The annual asthma exacerbations and exacerbations requiring emergency room visit/hospitalization were analyzed through a negative binomial regression model, with the logarithm of time at risk included as an offset variable. In PATHWAY, treatment group, baseline blood eosinophil count (≥ or < 250 cells/uL), and baseline ICS dose level (medium or high) were included as covariates. Rates are the total number of asthma exacerbation in each group / total person-year follow-up in each group with exact Poisson confidence intervals. In NAVIGATOR, treatment, region, age group, history of exacerbations were included as covariates and estimated marginal rates are presented from the model.

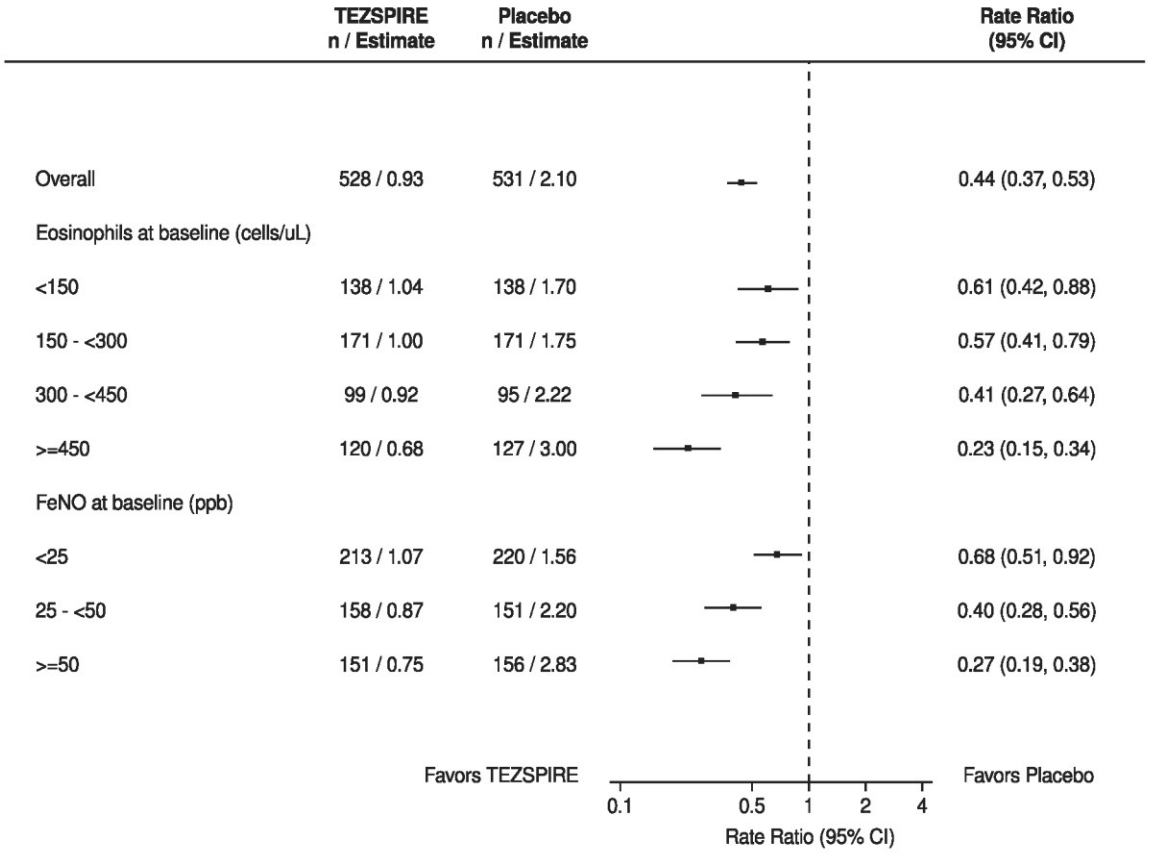
The time to first exacerbation was longer for the patients receiving Tezspire compared with placebo in NAVIGATOR (Figure 1). Similar results were seen in PATHWAY.

Figure 1 Kaplan-Meier Cumulative Incidence Curves for Time to First Exacerbation Through Week 52, NAVIGATOR



The results of an exploratory subgroup analysis from NAVIGATOR are presented in Figure 2 below. Patients receiving Tezspire experienced fewer exacerbations than those receiving placebo regardless of baseline levels of blood eosinophils or FeNO. Similar results were observed in PATHWAY. In NAVIGATOR, tezepelumab reduced the rate of exacerbations in subjects with baseline blood eosinophils < 300 cells/µL by 41% (rate ratio 0.59 [95% CI 0.46, 0.75]) and in subjects with baseline blood eosinophils ≥ 300 cells/µL by 70% (rate ratio 0.30 [95% CI 0.22, 0.40]). Treatment with tezepelumab also resulted in clinically meaningful reductions in the rate of exacerbations versus placebo irrespective of allergic status (allergic/non-allergic), when assessed categorically.

Figure 2 Annualized Asthma Exacerbation Rate Ratio Over 52 Weeks Across Different Baseline Biomarkers, NAVIGATOR



Lung Function

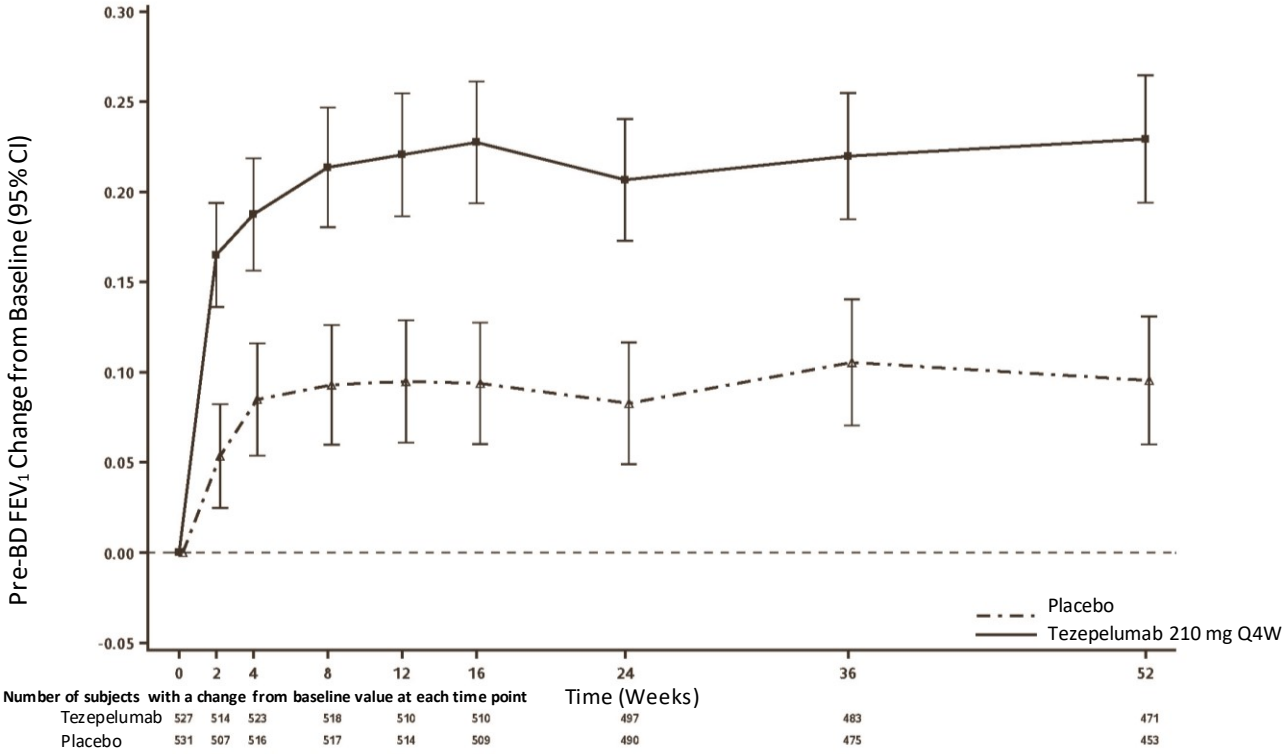
Compared with placebo, Tezspire provided clinically meaningful improvements in the mean change from baseline in FEV_1 in both PATHWAY and NAVIGATOR (Table 7).

Table 7 Mean Change from Baseline in Pre-Bronchodilator FEV_1 at Week 52, NAVIGATOR and PATHWAY

Trial	Treatment	LS Mean Change from Baseline (L)	Difference from Placebo (95% CI)
NAVIGATOR	Tezspire (N=527*)	0.23	0.13 (0.08, 0.18)
	Placebo (N=531*)	0.10	
PATHWAY	Tezspire (N=133*)	0.08	0.13 (0.03, 0.23)
	Placebo (N=138*)	-0.06	

* Number of patients contributing to the full analysis with at least 1 change from baseline value

Figure 3 Mean Change (95%CI) from Baseline in Pre-Bronchodilator FEV_1 (L) Over Time, NAVIGATOR



Patient Reported Outcomes

In both trials, more patients treated with Tezspire compared to placebo had a clinically meaningful improvement in ACQ-6 and AQLQ(S)+12. Clinically meaningful improvement (responder rate) for ACQ-6 and AQLQ(S)+12 was defined as improvement in score of 0.5 at end of trial. In NAVIGATOR, the ACQ-6 responder rate for Tezspire was 86% compared with 77% for placebo and the AQLQ(S)+12 responder rate for Tezspire was 78% compared with 72% for placebo. Similar findings were seen in PATHWAY.

Oral Corticosteroid Reduction

In an OCS-sparing trial, SOURCE, the effect of Tezspire on reducing the use of maintenance OCS was evaluated. The mean percent reduction in daily OCS dose from baseline at week 48 in subjects receiving Tezspire was 63.6% (median 100%) and placebo was 61.2% (median 75%) without losing asthma control. Reductions of 50% or higher in the OCS dose were observed in 55 (74%) patients receiving Tezspire compared to the 53 (70%) patients receiving placebo.

Adolescent Population

A total of 82 adolescents aged 12 to 17 with severe, uncontrolled asthma were enrolled in NAVIGATOR and received treatment with Tezspire (n=41) or placebo (n=41). Compared with placebo, clinically meaningful improvements in annualised asthma exacerbation (rate ratio 0.70; 95% CI 0.34, 1.46) and FEV_1 (LS mean change from placebo 0.17 L; 95% CI -0.01, 0.35) were observed in adolescents treated with Tezspire.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

In a 3-month repeat-dose toxicity study, male and female cynomolgus monkeys were administered tezepelumab by SC injection at doses of 0, 50, 100 or 300 mg/kg/week with some animals following on with a 5-month tezepelumab-free recovery phase. No tezepelumab-related adverse effects were observed. While a delay and/or reduction in immune reaction to an antigen challenge was observed at the 300 mg/kg/week dose level, this finding was not accompanied by changes indicative of infection and was considered non-adverse. Thus, the no-observed-adverse-effect level (NOAEL) was 300 mg/kg/week (the highest dose tested). Exposure at the NOAEL is 138-fold higher than the exposure in adult human patients and 105-fold higher than the exposure in adolescent human patients receiving 210 mg every 4 weeks, based on AUC.

Repeat-dose toxicity of tezepelumab was also evaluated in a 6-month study using the SC and intravenous (IV) routes of administration. Male and female cynomolgus monkeys were administered 0 (both IV and SC groups), 50 (both IV and SC groups), or 300 (SC only) mg/kg/week with some animals following on with a 5-month tezepelumab-free recovery phase. One female animal administered 50 mg/kg/week of tezepelumab IV was euthanized on Day 156 of the study due to poor clinical condition, which was attributed to vascular changes resulting from circulating immune complexes due to anti-drug antibodies to tezepelumab. No tezepelumab-related adverse effects were observed following SC dosing. Thus, the NOAEL following SC administration was 300 mg/kg/week (the highest dose tested). Exposure at the NOAEL for SC administration is 111-fold higher than the exposure in adult human patients and 85-fold higher than the exposure in adolescent human patients receiving 210 mg every 4 weeks, based on AUC.

Carcinogenicity

Tezepelumab is a monoclonal antibody, as such carcinogenicity studies have not been conducted to evaluate the carcinogenic potential of tezepelumab.

Genotoxicity

Tezepelumab is a monoclonal antibody, as such genotoxicity studies have not been conducted to evaluate the genotoxic potential of tezepelumab.

Reproductive and Developmental Toxicology

In an enhanced prenatal and postnatal development study conducted in cynomolgus monkeys, pregnant animals were administered tezepelumab by IV injection at doses of 0 (vehicle), 50, or 300 mg/kg/week from early gestation (gestation day 20 to 22) through delivery. No adverse effects on maternal health, pregnancy outcome, embryo-fetal development, or infant growth and development up to 6.5 months of age were observed. Tezepelumab was detected in infant serum throughout the post-natal period. The infant to maternal ratios of serum tezepelumab concentrations increased with increasing time during the post-natal period, indicating slower drug clearance in infants than in maternal animals. Tezepelumab was also detected in milk at concentrations <1% of the maternal serum concentrations. Comparison of maternal and infant serum ratios suggested that the majority of tezepelumab transfer to the infant occurred in utero

but transfer via milk cannot be excluded. Based on the results of this study the NOAEL for the maternal and developmental toxicity of tezepelumab is 300 mg/kg/week (the highest dose tested). Maternal exposure at the NOAEL was 168-fold higher than the exposure in human patients receiving 210 mg every 4 weeks, based on AUC.

Effects on male and female fertility have not been directly evaluated in animal studies. Examination of surrogate fertility parameters (menstrual cycle, semen analysis, organ weights, and microscopic pathology) was performed in sexually mature male and female cynomolgus monkeys as part of the 6-month repeat-dose toxicology study. There were no tezepelumab-related effects on these parameters at any dose in this study.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr TEZSPIRE™
Tezepelumab injection

Read this carefully before you start taking **TEZSPIRE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TEZSPIRE**.

What is TEZSPIRE used for?

- TEZSPIRE is a prescription medicine used with other asthma medicines for the maintenance treatment of severe asthma in people 12 years of age and older whose asthma is not controlled with their current asthma medicine.
- TEZSPIRE is not used to treat sudden breathing problems.

How does TEZSPIRE work?

TEZSPIRE works by blocking the action of thymic stromal lymphopoietin (TSLP), a protein that plays a role in causing the signs and symptoms of asthma.

TEZSPIRE may reduce the number of asthma attacks you experience, improve your breathing and reduce your asthma symptoms.

What are the ingredients in TEZSPIRE?

Medicinal ingredients: tezepelumab

Non-medicinal ingredients: glacial acetic acid, L-proline, polysorbate 80, sodium hydroxide, and water for injection.

TEZSPIRE comes in the following dosage form:

Solution for injection.

Each single-use, pre-filled syringe or pre-filled pen contains 210 mg of tezepelumab in 1.91 mL of solution.

Do not use TEZSPIRE if:

- you are allergic to tezepelumab or any of the other ingredients of this medicine. Check with your healthcare professional if you think, or you are not sure, if this applies to you.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEZSPIRE. Talk about any health conditions or problems you may have, including if you:

- have asthma that remains uncontrolled or worsens during treatment with TEZSPIRE.
- have had any symptoms of an allergic reaction (symptoms may vary, but can include breathing problems, hives, and rash). If you notice any of these signs, speak to your healthcare professional immediately.

- have a parasitic infection or if you live in an area where parasitic infections are common or if you are travelling to such a region. TEZSPIRE may weaken your ability to fight certain types of parasitic infections.
- are pregnant, think you may be pregnant, or plan to become pregnant. Do not use TEZSPIRE unless your healthcare professional tells you to. It is not known if TEZSPIRE can harm your unborn baby.
- are breast-feeding. TEZSPIRE may pass into breast milk. Your healthcare professional will discuss with you whether you should stop treatment with TEZSPIRE while you are breast-feeding, or if you should stop breast-feeding.

Other warnings you should know about:

TEZSPIRE is not a rescue medicine and should not be used to treat a sudden asthma attack.

TEZSPIRE is not approved for use in children below the age of 12.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

There are no known interactions with TEZSPIRE.

Tell your healthcare professional if you have recently had or are due to have a vaccination.

Do not suddenly stop taking your asthma medicines once you have started TEZSPIRE.

These medicines (especially ones called corticosteroids) must be stopped gradually, under the direct supervision of your doctor and based on your response to TEZSPIRE.

How to take TEZSPIRE:

- Always use TEZSPIRE exactly as your healthcare professional has told you. If you or your caregiver have any questions, talk to your healthcare professional.
- TEZSPIRE is given as an injection just under the skin (subcutaneously).
- Your healthcare professional should decide if you or your caregiver should inject TEZSPIRE. Before using your TEZSPIRE pre-filled syringe or pre-filled pen, your healthcare professional should show you or your caregiver how to use it the right way. Read the "INSTRUCTIONS FOR USE" for TEZSPIRE pre-filled syringe or pre-filled pen carefully before using TEZSPIRE and each time you get a refill. There may be new information.
- Do not share or use TEZSPIRE pre-filled syringe or pre-filled pen more than one time.
- Do not stop using TEZSPIRE without speaking to your healthcare professional first. Interrupting or stopping the treatment with TEZSPIRE may cause your asthma symptoms and attacks to come back.

Usual dose:

The recommended dose is 210 mg every 4 weeks.

Overdose:

If you think you, or a person you are caring for, have taken too much TEZSPIRE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you or your caregiver missed a dose, inject a dose as soon as possible. Continue your next injection on your usual injection day. If you did not notice that you have missed a dose until it is time for your next scheduled dose, then inject the next scheduled dose as planned. If you are not sure when to inject TEZSPIRE, contact your healthcare professional.

What are possible side effects from using TEZSPIRE?

These are not all the possible side effects you may have when taking TEZSPIRE. If you experience any side effects not listed here, tell your healthcare professional.

Symptoms can include:
Common (These may affect **up to 1 in 10 people**):

- Sore throat (pharyngitis)
- Injection site reaction (i.e. redness, swelling, and pain)
- Joint pain (arthralgia)
- Rash

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Do not use this medicine if it has been dropped or damaged, if the security seal on the carton has been broken or after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

Store between 2°C to 8°C (in a refrigerator) in the original package in order to protect from light. TEZSPIRE may be kept at room temperature (20˚C to 25˚C) in the original carton for a maximum of 30 days. Once TEZSPIRE has reached room temperature, do not put it back in the refrigerator. Throw away (dispose of) TEZSPIRE that has been stored at room temperature after 30 days.

Do not shake, freeze or expose to heat.

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

Keep out of reach and sight of children.

If you want more information about TEZSPIRE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.astrazeneca.ca, or by calling 1-800-668-6000.
- This Patient Medication Information is current at the time of printing. The most up-to-date version can be found at www.astrazeneca.ca

This leaflet was prepared by AstraZeneca Canada Inc., Mississauga, Ontario L4Y 1M4.

Last revised: July 28, 2022

INSTRUCTIONS FOR USE – PRE-FILLED SYRINGE

℞ TEZSPIRE™

Tezepelumab injection, Subcutaneous use
Single-use, Pre-filled Syringe

This Instructions for Use contains information on how to inject TEZSPIRE.

Before using your TEZSPIRE pre-filled syringe, your healthcare provider should show you or your caregiver how to use it the right way.

Read this Instructions for Use before you start using your TEZSPIRE pre-filled syringe and each time you get a refill. There may be new information. This information should not replace talking to your healthcare provider about your medical condition and your treatment.

If you or your caregiver have any questions, talk to your healthcare provider.

Important information you need to know before injecting TEZSPIRE

Store TEZSPIRE in a refrigerator between 2°C to 8°C in its original carton until you are ready to use it to protect it from light. TEZSPIRE may be kept at room temperature between 20°C to 25°C in the original carton for a maximum of 30 days.

When TEZSPIRE has reached room temperature, **do not** put it back in the refrigerator.

Throw away (dispose of) TEZSPIRE that has been stored at room temperature for more than 30 days.

Do not use your TEZSPIRE pre-filled syringe if:

- it has been frozen
- it has been dropped or damaged
- the security seal on the carton has been broken
- the expiration date (EXP) has passed

Do not shake your pre-filled syringe.

Do not share, or use your pre-filled syringe more than 1 time.

Do not expose your TEZSPIRE pre-filled syringe to heat.

If any of the above happens, throw away the syringe in a puncture-resistant (sharps) container and use a new TEZSPIRE pre-filled syringe.

Each TEZSPIRE pre-filled syringe contains 1 dose of TEZSPIRE that can only be used 1 time.

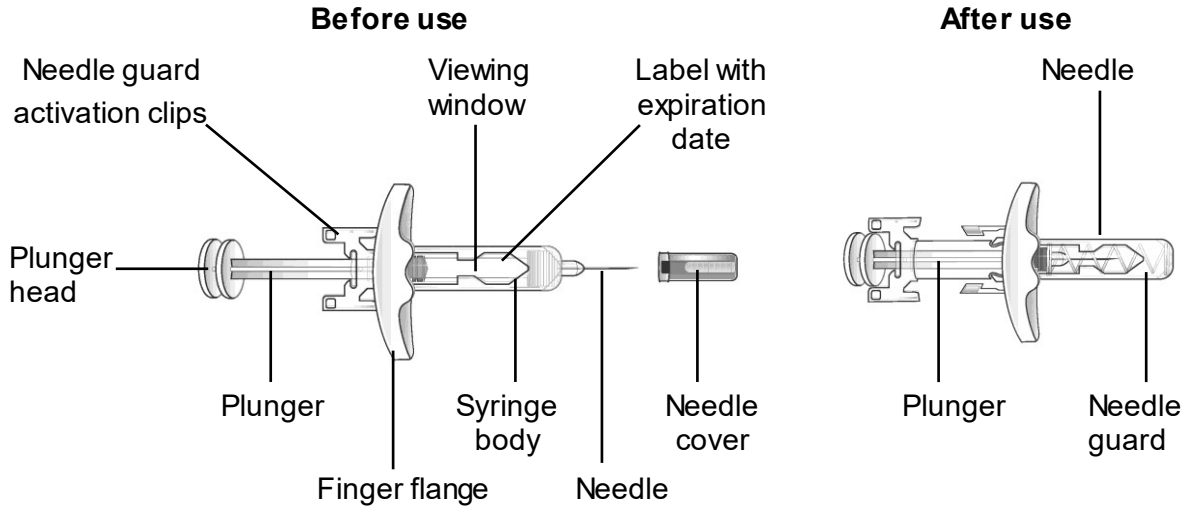
Keep TEZSPIRE pre-filled syringe and all medicines out of the sight and reach of children.

TEZSPIRE is given only as an injection under the skin (subcutaneous).

Your TEZSPIRE pre-filled syringe

Do not remove the needle cover until Step 7 of these instructions when you are ready to inject TEZSPIRE.

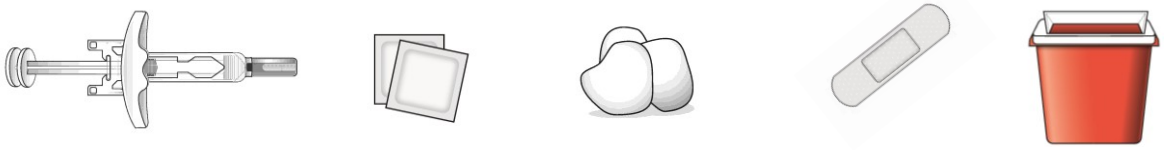
Do not touch the needle guard activation clips. This will keep you from activating the safety device (needle guard) too soon.



Preparing to inject TEZSPIRE

Step 1 – Gather supplies

- 1 TEZSPIRE pre-filled syringe from the refrigerator
- 1 alcohol wipe
- 1 cotton ball or gauze
- 1 small bandage (optional)
- 1 puncture-resistant (sharps) disposal container. See Step 10 for instructions on how to throw away (dispose of) the used TEZSPIRE pre-filled syringe safely.



Pre-filled syringe | Alcohol wipe | Cotton ball or gauze | Bandage | Sharps disposal container

Step 2 – Prepare to use your TEZSPIRE pre-filled syringe

Let TEZSPIRE come to room temperature between 20°C to 25°C for about 60 minutes or longer (up to a maximum of 30 days) before giving the injection.

Keep the pre-filled syringe in its original carton to protect it from light.

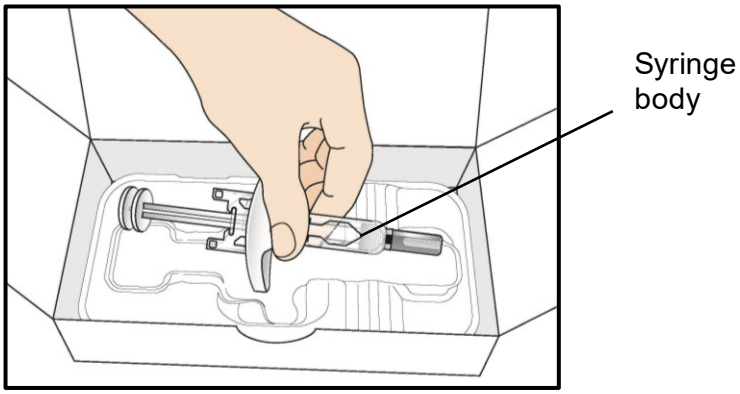
Do not warm the pre-filled syringe in any other way. For example, **do not** warm it in a microwave or hot water, in direct sunlight, or near other heat sources.

Do not put TEZSPIRE back in the refrigerator after it has reached room temperature. Throw away (dispose of) TEZSPIRE that has been stored at room temperature for more than 30 days.

Do not remove the needle cover until Step 7.

Step 3 – Remove pre-filled syringe

Grab the syringe body to remove the pre-filled syringe from its tray. **Do not** grab the pre-filled syringe by the plunger.



Step 4 – Check the pre-filled syringe

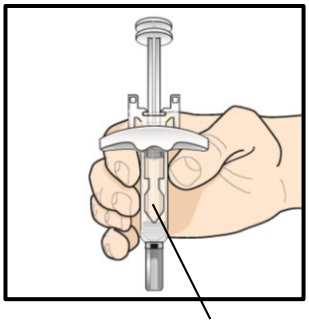
Check the pre-filled syringe for damage. Do not use the pre-filled syringe if the pre-filled syringe is damaged.

Check the expiration date on the pre-filled syringe. **Do not** use the pre-filled syringe if the expiration date has passed.

Look at the liquid through the viewing window. The liquid should be clear and colourless to light yellow.

Do not inject TEZSPIRE if the liquid is cloudy, discoloured, or contains large particles.

You may see small air bubbles in the liquid. This is normal. You do not need to do anything about it.



Injecting TEZSPIRE

Step 5 – Choose an injection site

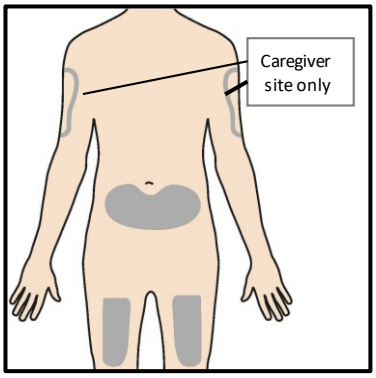
If you are giving yourself the injection, the **recommended injection site** is the front of your thigh or the lower part of your stomach (abdomen). **Do not** inject yourself in the arm.

A caregiver may inject you in the upper arm, thigh, or abdomen.

For each injection, choose a different site that is at least 3 cm away from where you last injected.

Do not inject:

- into the 5 cm area around your belly button
- where the skin is tender, bruised, scaly or hard
- into scars or damaged skin
- through clothing



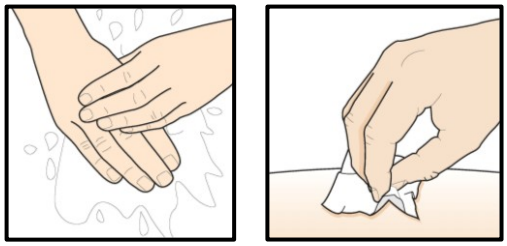
Step 6 – Wash your hands and clean the injection site

Wash your hands well with soap and water.

Clean the injection site with an alcohol wipe in a circular motion. Let it air dry.

Do not touch the cleaned area before injecting.

Do not fan or blow on the cleaned area.



Step 7 – Pull off the needle cover

Do not remove the cap until you are ready to inject.

Hold the syringe body with 1 hand, and carefully pull the needle cover straight off with your other hand.

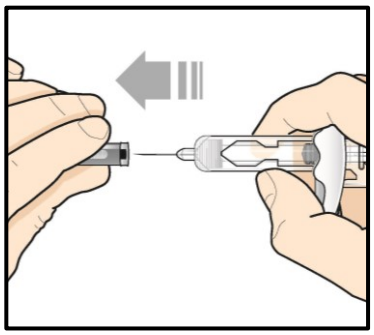
Do not hold the plunger or plunger head while removing the needle cover.

Put the needle cover to the side and throw it away later.

You may see a drop of liquid at the end of the needle. This is normal.

Do not touch the needle or let it touch any surface.

Do not put the needle cover back on the syringe.



Step 8 – Inject TEZSPIRE

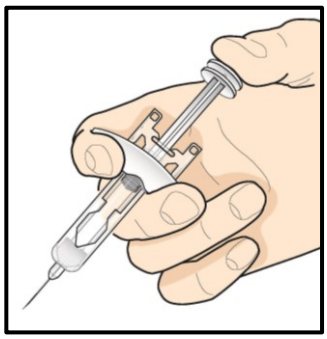
Hold the pre-filled syringe in 1 hand as shown.

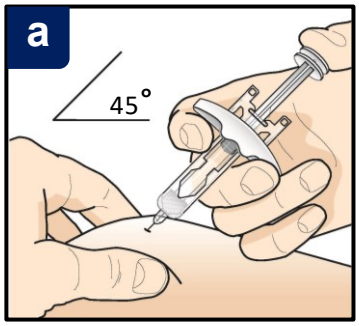
Use your other hand to gently pinch and hold the area of skin where you want to inject. This will make the skin more firm.

Do not press down on the plunger head until the needle is inserted into the skin.

Do not pull back on the plunger head at any time.

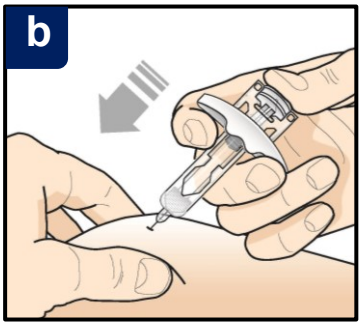
Inject TEZSPIRE by following the steps in figures **a**, **b** and **c**.





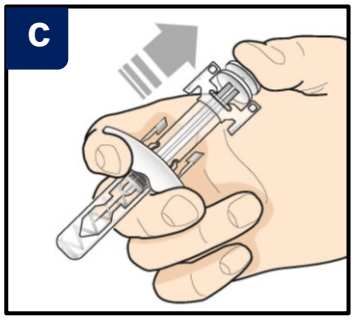
Using a 45 degree angle, fully insert the needle into the pinched skin.

Do not try to change the position of the pre-filled syringe after you insert it into the skin.



Use your thumb to push down on the plunger head.

Keep pushing until it is down as far as it will go to make sure you inject all of the medicine.



Keep your thumb pressed down on the plunger head as you take the needle out of the skin.

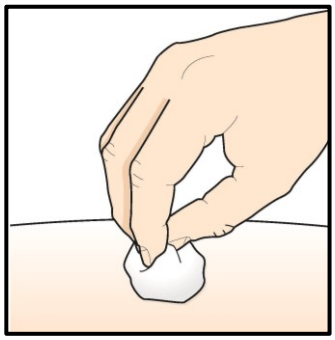
Slowly let go of the plunger until the needle guard covers the needle.

Step 9 – Check the injection site

There may be a small amount of blood or liquid where you injected. This is normal.

Gently hold pressure over your skin with a cotton ball or gauze until the bleeding stops.

Do not rub the injection site. If needed, cover the injection site with a small bandage.



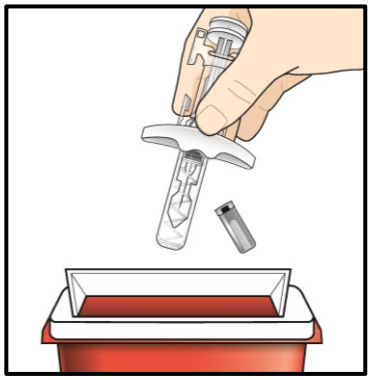
Disposing of TEZSPIRE

Step 10 – Dispose of the used pre-filled syringe safely

Each pre-filled syringe contains a single dose of TEZSPIRE and **cannot be used again**. **Do not** put the needle cover back on the pre-filled syringe.

Put your used syringe and needle cover in a **sharps disposal container** right away after use. Put other used supplies in your household trash.

Do not throw away the pre-filled syringe in your household trash.



Disposal guidelines

Dispose of the full container as instructed by your healthcare provider or pharmacist.

Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this.

Do not recycle your used sharps disposal container.

INSTRUCTIONS FOR USE – PRE-FILLED PEN

℞ TEZSPIRE™

Tezepelumab injection, Subcutaneous use
Single-use, Pre-filled Pen

This Instructions for Use contains information on how to inject TEZSPIRE.

Before using your TEZSPIRE pre-filled pen, your healthcare provider should show you or your caregiver how to use it the right way.

Read this Instructions for Use before you start using your TEZSPIRE pre-filled pen and each time you get a refill. There may be new information. This information should not replace talking to your healthcare provider about your medical condition and your treatment.

If you or your caregiver have any questions, talk to your healthcare provider.

Important information you need to know before injecting TEZSPIRE

Store TEZSPIRE in a refrigerator between 2°C to 8°C in its original carton until you are ready to use it to protect it from light. TEZSPIRE may be kept at room temperature between 20°C to 25°C in the original carton for a maximum of 30 days.

When TEZSPIRE has reached room temperature, **do not** put it back in the refrigerator.

Throw away (dispose of) TEZSPIRE that has been stored at room temperature for more than 30 days.

Do not use your TEZSPIRE pre-filled pen if:

- it has been frozen
- it has been dropped or damaged
- the security seal on the carton has been broken
- the expiration date (EXP) has passed

Do not shake your pre-filled pen.

Do not share, or use your pre-filled pen more than 1 time.

Do not expose your TEZSPIRE pre-filled pen to heat.

If any of the above happens, throw away the pre-filled pen in a puncture-resistant (sharps) container and use a new TEZSPIRE pre-filled pen.

Each TEZSPIRE pre-filled pen contains 1 dose of TEZSPIRE that can only be used 1 time.

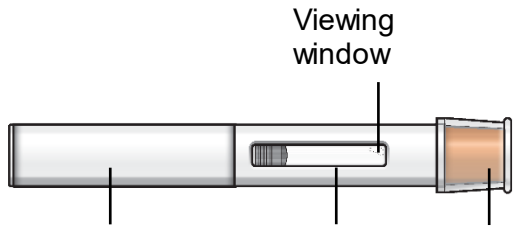
Keep TEZSPIRE pre-filled pen and all medicines out of the sight and reach of children.

TEZSPIRE is given only as an injection under the skin (subcutaneous).

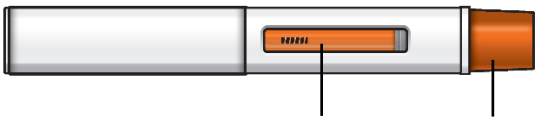
Your TEZSPIRE pre-filled pen

Do not remove the cap until Step 6 of these instructions when you are ready to inject TEZSPIRE.

Before use



After use



Preparing to inject TEZSPIRE

Step 1 – Gather supplies

- 1 TEZSPIRE pre-filled pen from the refrigerator
- 1 alcohol wipe
- 1 cotton ball or gauze
- 1 small bandage (optional)
- 1 puncture-resistant (sharps) disposal container. See Step 10 for instructions on how to throw away (dispose of) the used TEZSPIRE pre-filled pen safely.

Pre-filled pen

Alcohol wipe

Cotton ball or gauze

Bandage

Sharps disposal container

Step 2 – Prepare to use your TEZSPIRE pre-filled pen

Let TEZSPIRE come to room temperature between 20°C to 25°C for about 60 minutes or longer (up to a maximum of 30 days) before giving the injection.

Keep the pre-filled pen in its original carton to protect it from light.

Do not warm the pre-filled pen in any other way. For example, **do not** warm it in a microwave or hot water, in direct sunlight, or near other heat sources.

Do not put TEZSPIRE back in the refrigerator after it has reached room temperature. Throw away (dispose of) TEZSPIRE that has been stored at room temperature for more than 30 days.

Do not remove the cap until Step 6.

Step 3 – Remove and check the pre-filled pen

Grab the middle of the pre-filled pen body to remove the pre-filled pen from its tray.

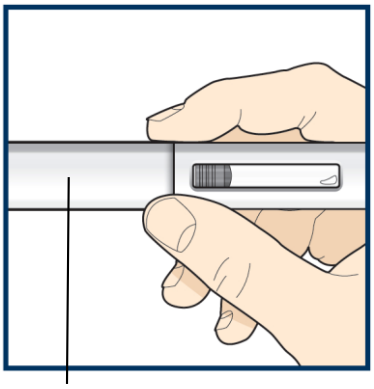
Check the pre-filled pen for damage. Do not use the pre-filled pen if the pre-filled pen is damaged.

Check the expiration date on the pre-filled pen. **Do not** use the pre-filled pen if the expiration date has passed.

Look at the liquid through the viewing window. The liquid should be clear and colourless to light yellow.

Do not inject TEZSPIRE if the liquid is cloudy, discoloured, or contains large particles.

You may see small air bubbles in the liquid. This is normal. You do not need to do anything about it.



Injecting TEZSPIRE

Step 4 – Choose an injection site

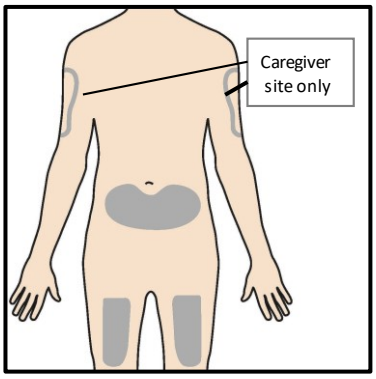
If you are giving yourself the injection, the **recommended injection site** is the front of your thigh or the lower part of your stomach (abdomen). **Do not** inject yourself in the arm.

A caregiver may inject you in the upper arm, thigh, or abdomen.

For each injection, choose a different site that is at least 3 cm away from where you last injected.

Do not inject:

- into the 5 cm area around your belly button
- where the skin is tender, bruised, scaly or hard
- into scars or damaged skin



- through clothing

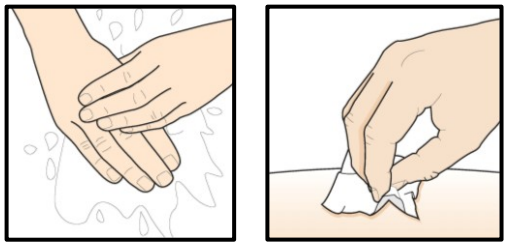
Step 5 – Wash your hands and clean the injection site

Wash your hands well with soap and water.

Clean the injection site with an alcohol wipe in a circular motion. Let it air dry.

Do not touch the cleaned area before injecting.

Do not fan or blow on the cleaned area.



Step 6 – Pull off the cap

Do not remove the cap until you are ready to inject.

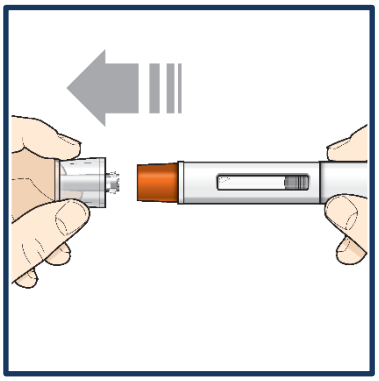
Hold the pre-filled pen body with 1 hand, and carefully pull the cap straight off with your other hand.

Put the cap to the side and throw it away later.

The orange needle guard is now exposed. The orange needle guard is there to prevent you from touching the needle.

Do not touch the needle or push on the orange needle guard with your finger.

Do not put the cap back on the pre-filled pen. You could cause the injection to happen too soon or damage the needle.

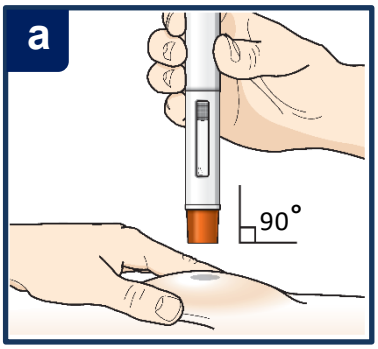


Step 7 – Inject TEZSPIRE

Follow your healthcare provider's instruction on how to inject. You can either gently pinch the skin at the injection site or give the injection without pinching the skin.

Inject TEZSPIRE by following the steps in figures **a**, **b**, **c** and **d**.

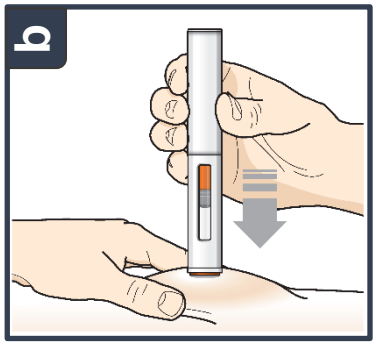
When injecting, you will hear the first click that tells you the injection has started. Press and hold the pre-filled pen for 15 seconds until you hear the **second click.**



Do not change the position of the pre-filled pen after the injection has started.

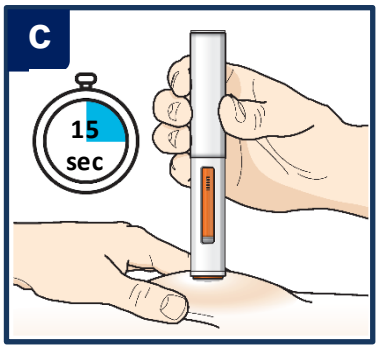
Position the pre-filled pen.

- Place the orange needle guard flat against your skin (90-degree angle).
- Make sure you can see the viewing window.



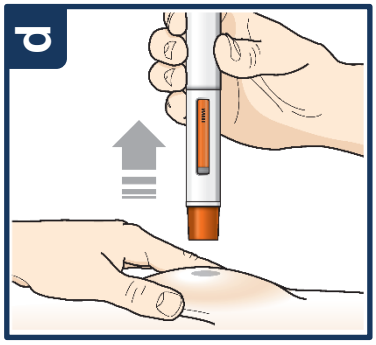
Press down firmly until you cannot see the orange needle guard.

- You will hear the first **'click'**, this tells you the injection has started.
- The orange plunger will move down in the viewing window during the injection.



Hold down firmly for about 15 seconds.

- You will hear a second **'click'**, this tells you the injection has finished.
- The orange plunger will fill the viewing window.



After you have completed your injection, lift the pre-filled pen straight up.

- The orange needle guard will slide down and lock into place over the needle.

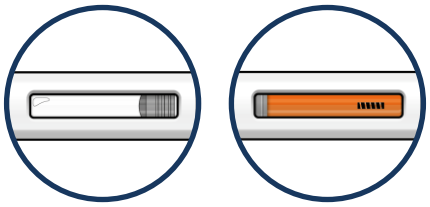
Step 8 – Check the viewing window

Check the viewing window to make sure all the medicine has been injected.

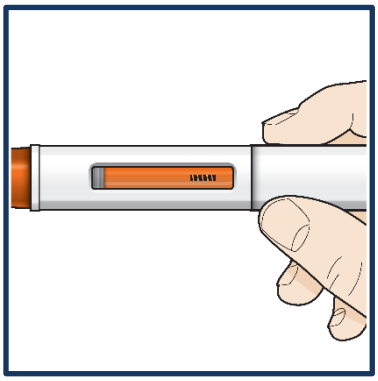
If the orange plunger rod does not fill the viewing window, you may not have received the full dose.

If this happens or if you have any other concerns, contact your healthcare provider.

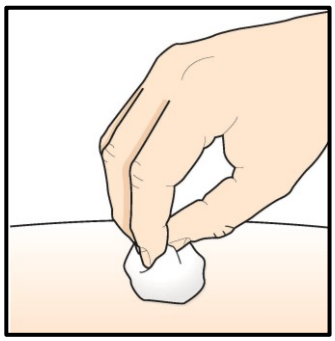
Before injection



After injection



Step 9 – Check the injection site



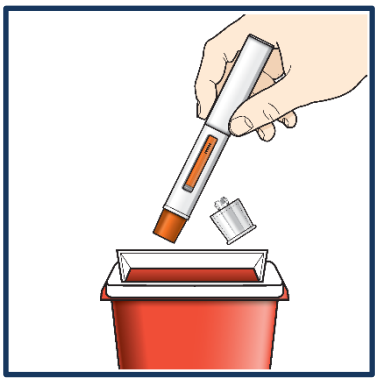
There may be a small amount of blood or liquid where you injected. This is normal.

Gently hold pressure over your skin with a cotton ball or gauze until the bleeding stops.

Do not rub the injection site. If needed, cover the injection site with a small bandage.

Disposing of TEZSPIRE

Step 10 – Dispose of the used pre-filled pen safely



Each pre-filled pen contains a single dose of TEZSPIRE and **cannot be used again**. **Do not** put the cap back on the pre-filled pen.

Put your used pre-filled pen and cap in a **sharps disposal container** right away after use. Put other used supplies in your household trash.

Do not throw away the pre-filled pen in your household trash.

Disposal guidelines

Dispose of the full container as instructed by your healthcare provider or pharmacist.

Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this.

Do not recycle your used sharps disposal container.