PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrFASENRA®

Benralizumab Injection

30 mg/mL solution for subcutaneous injection

Anti-eosinophil
(anti-interleukin-5 receptor alpha monoclonal antibody)

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RECENT MAJOR LABEL CHANGES

Not applicable.

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

FASENRA (benralizumab injection) is indicated as an add-on maintenance treatment of adult patients with severe eosinophilic asthma.

FASENRA is not indicated for other eosinophilic conditions or for relief of acute bronchospasm or status asthmaticus (see WARNINGS AND PRECAUTIONS).

FASENRA should be administered by a qualified healthcare professional who is experienced in the monitoring of signs and symptoms of hypersensitivity after administration of biologic agents and prepared to manage anaphylaxis that can be life-threatening (see WARNINGS AND PRECAUTIONS, Hypersensitivity and DOSAGE AND ADMINISTRATION).

1.1 Pediatrics

Pediatrics (< 18 years of age): FASENRA is not indicated in the pediatric population, as the efficacy and safety of FASENRA has not been established in patients less than 18 years of age (see WARNINGS AND PRECAUTIONS, Special Populations).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): There is limited experience with FASENRA in patients 65 years of age and older. No overall differences in efficacy or safety of FASENRA were observed between geriatric and adult patients treated with FASENRA in clinical trials. Sensitivity of some older individuals, however, cannot be excluded (see WARNINGS AND PRECAUTIONS, Special Populations and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

2 CONTRAINDICATIONS

FASENRA (benralizumab injection) is contraindicated in patients who are hypersensitive to benralizumab, or to any ingredient(s) in the formulation (see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

FASENRA (benralizumab injection) is for subcutaneous use only.

FASENRA should be administered by a qualified healthcare professional who is experienced in the monitoring of signs and symptoms of hypersensitivity after administration of biologic agents and prepared to manage anaphylaxis that can be life-threatening. Do not administer into areas where the skin is tender, bruised, erythematous, or hardened. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended (see WARNINGS AND PRECAUTIONS).

3.2 Recommended Dose and Dosage Adjustment

The recommended dose of FASENRA is 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter by subcutaneous injection into the upper arm, thigh, or abdomen.

Pediatrics (< 18 years of age): FASENRA is not indicated for use in the pediatric population as the efficacy and safety of FASENRA has not been established in patients 12 to 18 years of age (see CLINICAL TRIALS). No studies have been conducted in children below 12 years of age.

Geriatrics (≥ 65 years of age): No dose adjustment is required for elderly patients (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

Renal Impairment: No dose adjustment is required for patients with renal impairment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

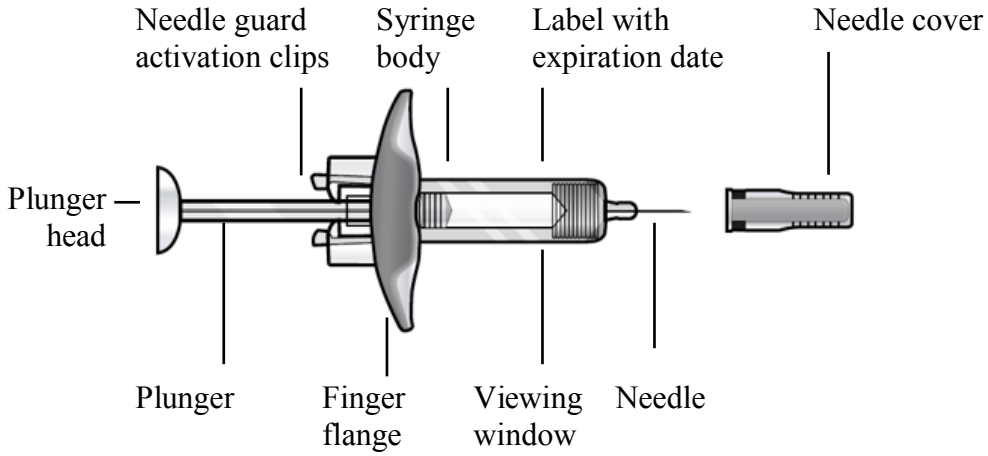
Hepatic Impairment: No dose adjustment is required for patients with hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

3.3 Administration

Prior to administration, warm FASENRA by placing the product at room temperature. This generally takes 30 minutes from a refrigerated storage condition. Administer FASENRA within 24 hours after taking out of the refrigerator or discard unused drug into sharps container.

Instructions for Prefilled Syringe with Needle Safety Guard
Figure 1 identifies the prefilled syringe components for use in the administration steps.

Figure 1

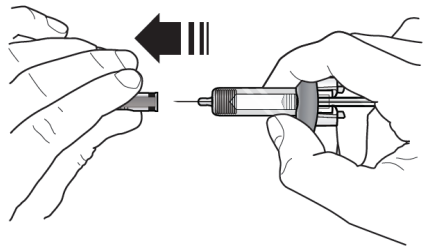


Do not touch the needle guard activation clips to prevent premature activation of the needle safety guard.

Prepare Syringe:

1 **Grasp the syringe body** (not the plunger) to remove prefilled syringe from the tray (inside the carton packaging). Check the expiration date on the syringe. Visually inspect FASENRA for particulate matter and/or discolouration prior to administration. FASENRA is clear to opalescent, colourless to yellow, and may contain translucent or white to off-white particles. Do not use FASENRA if liquid is cloudy, discoloured, or if it contains large particles or foreign particulate matter. The syringe may contain a small air bubble; this is normal. **Do not** expel the air bubble prior to administration.

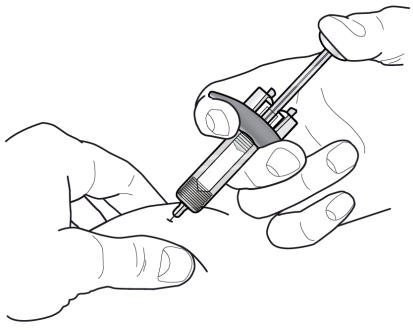
2



Do not remove needle cover until ready to inject. Hold the syringe body and remove the needle cover by pulling straight off. Do not hold the plunger or plunger head while removing the needle cover as the plunger may move. If prefilled syringe is damaged or contaminated (e.g., dropped without needle cover in place), discard and use a new prefilled syringe.

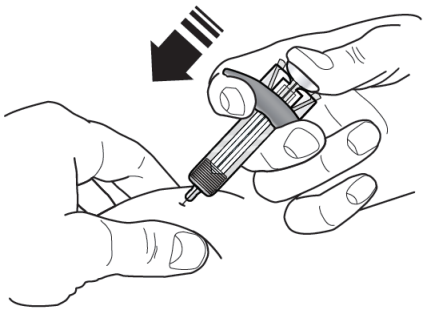
How to administer a dose:

1



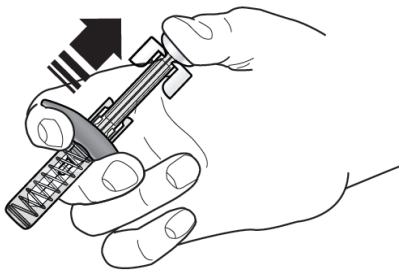
Gently pinch the skin and fully insert the needle at the recommended injection site (i.e., upper arm, thigh, or abdomen).

2



Inject all of the medication by pushing down on the plunger all the way until the plunger head is **completely between** the needle guard activation clips. **This is necessary to activate the needle guard.**

After injection, maintain pressure on the plunger head and remove the needle from the skin. Release pressure on the plunger head to allow the needle guard to cover the needle. **Do not re-cap the prefilled syringe.** Discard the used syringe into a sharps container.



3.4 Missed Dose

If a dose is missed or the patient is unable to keep an appointment for one of the injections, the missed dose should be administered as soon as possible.

4 OVERDOSAGE

Doses of up to 200 mg were administered subcutaneously in clinical trials to patients with asthma without evidence of dose-related toxicities.

There is no specific treatment for an overdose with FASENRA (benralizumab injection). If overdose occurs, the patient should be monitored for any signs or symptoms of adverse effects and given appropriate supportive symptomatic treatment.

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

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
By subcutaneous injection	30 mg/mL solution in a 1 mL single-dose prefilled syringe	L-histidine; L-histidine hydrochloride monohydrate; α,α-trehalose dihydrate; and polysorbate 20; and Water for Injection.

FASENRA (benralizumab injection) is available in a pack containing one single-dose, single use, sterile prefilled syringe.

Each prefilled syringe contains 30 mg benralizumab in 1 mL (30 mg/mL). The prefilled syringe is comprised of a type I glass barrel with a staked 29 gauge 12.7 mm stainless steel needle, rigid needle shield and FluoroTec-coated plunger stopper in a passive safety device to prevent needle stick injuries (see DOSAGE AND AMINISTRATION, Figure 1).

6 DESCRIPTION

FASENRA (benralizumab injection) is a targeted, humanized monoclonal antibody (IgG1, kappa) that selectively binds to the alpha subunit of the human interleukin-5 receptor (IL-5Rα) with a low dissociation constant. Benralizumab is produced in Chinese hamster ovary cells by recombinant DNA technology. Benralizumab has a molecular weight of approximately 150 kDa.

7 WARNINGS AND PRECAUTIONS

General

Acute Asthma Symptoms or Deteriorating Disease: FASENRA (benralizumab injection) should not be used to treat acute asthma symptoms or acute exacerbations. **Do not use FASENRA 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 with FASENRA.

Corticosteroid Reduction:
Abrupt discontinuation of corticosteroids after initiation of FASENRA 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.

Infection

Eosinophils may be involved in the immunological response to some helminth infections. Patients with pre-existing helminth infections were excluded from participation in clinical trials. It is unknown if FASENRA may influence a patient's response against helminth infections. Patients with pre-existing helminth infections should be treated for their infection prior to therapy with FASENRA.

If patients become infected while receiving treatment with FASENRA and do not respond to anti-helminth treatment, discontinue treatment with FASENRA until infection resolves.

Sensitivity/Resistance

Hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred following administration of FASENRA. These reactions generally occur within hours of administration, but in some instances have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, FASENRA should be discontinued (see CONTRAINDICATIONS).

Sexual Health

Fertility: No data are available on the effect of FASENRA on human fertility. A study in monkeys

did not show any effects on reproductive organs or reproductive parameters (see NON-CLINICAL TOXICOLOGY).

7.1 Special Populations

7.1.1 Pregnant Women

No studies have been conducted with FASENRA in pregnant women. In clinical trials there were too few pregnancies to inform on maternal and fetal health and developmental outcomes.
A study in monkeys showed that benralizumab is pharmacologically active in infants exposed during organogenesis through parturition. Systemic exposure to benralizumab and suppression of eosinophil counts were observed in offspring of exposed animals. Animal studies did not demonstrate any additional effects on pregnancy or neonatal/infant development (see NON-CLINICAL TOXICOLOGY).

Animal studies are not always predictive of human response; therefore, it is not known whether FASENRA can cause fetal harm when administered to a pregnant woman.

FASENRA should not be used by pregnant women unless the expected benefit to the mother justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while receiving FASENRA and for up to 4 months after treatment is stopped.

Pregnancy Registry
To monitor maternal-fetal outcomes of pregnant women exposed to FASENRA, a pregnancy registry has been established. Healthcare professionals are encouraged to register patients, and pregnant women are encouraged to enroll themselves by calling 1-877-311-8972 or visiting http://www.mothertobaby.org.

7.1.2 Breast-feeding

There are no data regarding the presence of FASENRA in human breast milk, the effects on the breastfed infant, or the effects on milk production. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from benralizumab therapy taking into account the benefit of breast-feeding for the infant and the benefit of therapy for the mother.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): FASENRA is not indicated for use in the pediatric population as the efficacy and safety of FASENRA has not been established in patients 12 to 18 years of age (see CLINICAL TRIALS). Limited number of adolescent subjects (N=108) were enrolled in the FASENRA pivotal asthma exacerbation studies. No studies have been conducted in children below 12 years of age.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Of the total number of patients in clinical trials of benralizumab, 13% were 65 years of age and older, while 0.4% were 75 years of age and older. No overall differences in efficacy or safety were observed between these patients and adult patients. Sensitivity of some older individuals, however, cannot be excluded.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In clinical studies that included patients with severe asthma with an eosinophilic phenotype, the most commonly reported adverse reactions during treatment were headache, pharyngitis, pyrexia, and hypersensitivity reactions.

Hypersensitivity reactions may occur within hours or days of being treated with FASENRA (benralizumab injection), including swelling of the face, mouth, and tongue; fainting, dizziness, or light-headedness; hives; breathing problems; and rash.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials 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 is useful for identifying drug-related adverse events and for approximating rates.

Across three phase 3 studies (SIROCCO, CALIMA, and ZONDA), 1,808 patients received at least 1 dose of FASENRA (see CLINICAL TRIALS). These data described below reflect exposure to FASENRA in 1,663 patients with severe asthma, including 1,556 exposed for at least 24 weeks and 1,387 exposed for at least 48 weeks. The safety exposure for FASENRA is derived from phase 3 placebo-controlled studies (SIROCCO and CALIMA) from 48 weeks duration [FASENRA every 4 weeks (n = 841), FASENRA every 4 weeks for 3 doses, then every 8 weeks (n = 822), and placebo (n = 847)]. While a dosing regimen of FASENRA every 4 weeks was included in clinical trials, FASENRA administered every 4 weeks for 3 doses, then every 8 weeks thereafter is the recommended dose (see DOSAGE AND ADMINISTRATION).

Adverse events that occurred at greater than or equal to 1% incidence are shown in Table 2.

Table 2 Adverse events with ≥1% incidence with FASENRA and ≥1% more common with FASENRA than placebo in patients with severe eosinophilic asthma (SIROCCO and CALIMA)

	FASENRA n=822 n (%)	Placebo n=847 n (%)
General disorders and administration site conditions		
Pyrexia	23 (3%)	13 (2%)
Infections & Infestations		
Pharyngitis	33 (4%)	21 (2%)
Musculoskeletal and connective tissue disorders		
Arthralgia	30 (4%)	19 (2%)
Myalgia	16 (2%)	7 (1%)

Nervous system disorders		
Headache	68 (8%)	52 (6%)
Respiratory, thoracic and mediastinal disorders		
Cough	27 (3%)	17 (2%)

Immunogenicity: Treatment with FASENRA, like other monoclonal antibodies, may result in an anti-drug antibody (ADA) response (see ACTION AND CLINICAL PHARMACOLOGY, Immunogenicity). However, there is no apparent correlation of ADA development to efficacy or adverse events.

Phase 3 oral corticosteroid-reduction trial (ZONDA)
In ZONDA, 73 patients were treated with at least one dose of FASENRA, as per the recommended dosing regimen, while taking a daily oral corticosteroid (OCS) (7.5 to 40mg per day) in addition to regular use of high-dose ICS and LABA. Numerically higher incidence of headache and pyrexia were reported in this treatment group when compared to placebo. The frequencies for the remaining adverse reactions with FASENRA were similar to placebo. The safety results in ZONDA were similar to those observed in SIROCCO and CALIMA.

Adverse drug reactions (events considered to be possibly related to treatment with benralizumab) were identified following evaluation of all data from two randomized placebo controlled trials and include headache, pharyngitis (Pharyngitis was defined by the following grouped preferred terms: 'Pharyngitis', 'Pharyngitis bacterial', 'Viral pharyngitis', 'Pharyngitis streptococcal'), pyrexia, hypersensitivity reactions (Hypersensitivity Reactions were defined by the following grouped preferred terms: 'Urticaria', 'Urticaria papular', and 'Rash') and injection site reactions (all common; ≥1/100 to <1/10).

Less Common Clinical Trial Adverse Events
In addition to the events shown in Table 2, adverse events reported less commonly (defined as less than 1% in the FASENRA Q8W treatment group) in SIROCCO and CALIMA that were reported in 2 or more patients receiving FASENRA Q8W compared to no reports in patients receiving placebo are summarized below.

Blood and lymphatic system disorders: leukopenia, lymphadenopathy

Cardiac disorders: atrial fibrillation

Endocrine disorders: adrenal insufficiency

Eye disorders: conjunctival haemorrhage, eye haemorrhage

Gastrointestinal disorders: abdominal distension

General disorders and administration site conditions: chest pain, chills, feeling cold, hyperpyrexia, hyperthermia, injection site papule, pain

Hepatobiliary disorders: cholecystitis

Immune system disorders: food allergy

Infections and infestations: appendicitis, gingivitis, viral sinusitis

Injury, poisoning and procedural complications: arthropod bite, arthropod sting, eye injury, meniscus injury, stab wound

Investigations: bacterial test positive, blood alkaline phosphatase increased

Musculoskeletal and connective tissue disorders: arthritis, exostosis

Nervous system disorders: neuralgia

Psychiatric disorders: nervousness, panic attack, sleep disorder

Renal and urinary disorders: haematuria

Reproductive system and breast disorders: dysmenorrhea, ovarian cyst, pelvic pain, uterine polyp

Respiratory, thoracic and mediastinal disorders: nasal turbinate hypertrophy, respiratory tract inflammation

Skin and subcutaneous tissue disorders: dermatitis allergic

Vascular disorders: essential hypertension, haematoma, hypotension, lymphoedema, orthostatic hypotension, peripheral coldness

8.3 Post-Market Adverse Reactions

There is no post-market experience for FASENRA.

9 DRUG INTERACTIONS

9.1 Overview

No formal interaction studies have been conducted with FASENRA (benralizumab injection).

Cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of benralizumab. There is no evidence of IL-5Rα expression on hepatocytes and eosinophil depletion does not produce chronic systemic alterations of proinflammatory cytokines.

9.2 Drug-Drug Interactions

No formal drug-drug interaction studies have been conducted. An effect of benralizumab on the pharmacokinetics of co-administered medications is not expected. Based on the population analysis, commonly co-administered medications had no effect on benralizumab clearance in patients with asthma.

9.3 Drug-Food Interactions

FASENRA is administered as a subcutaneous injection. Interactions with food are therefore not applicable.

9.4 Drug-Herb Interactions

No formal drug-herb interaction studies have been conducted.

9.5 Drug-Laboratory Test Interactions

No formal drug-laboratory test interaction studies have been conducted.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

FASENRA (benralizumab injection) is a targeted, humanized afucosylated, monoclonal antibody (IgG1, kappa) that binds to the alpha subunit of the human interleukin-5 receptor (IL-5Rα) with a dissociation constant of 16 pM. The IL-5 receptor is expressed on the surface of eosinophils and basophils. The results of *in vitro* studies have also shown that the absence of fucose in the Fc domain of benralizumab results in higher affinity (45.5 nM) for FcγRIII receptors, which are expressed on immune effectors cells such as natural killer cells. *In vitro*, benralizumab induces apoptosis of eosinophils and basophils through enhanced antibody-dependent cell-mediated cytotoxicity (ADCC).

Inflammation is an important component in the pathogenesis of asthma. Eosinophils and other cell types (e.g., mast cells, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in inflammation in asthma. Benralizumab reduces eosinophilic inflammation through enhanced ADCC; however, the exact mechanism of benralizumab action in asthma has not been definitively established.

10.2 Pharmacodynamics

Dose-dependent reductions in blood eosinophils were observed following SC administration of benralizumab in asthma patients. In a 52-week Phase 2 dose-ranging trial, asthma patients received 1 of 3 doses of benralizumab [2 mg (n=81), 20 mg (n=81), or 100 mg (n=222)] administered every 4 weeks for the first 3 doses followed by every 8 weeks thereafter or placebo (n=222). At the time of the last dose (Week 40), median blood eosinophil counts were 170/μL, 100/μL, 50/μL, and 40/μL for placebo, 2, 20, and 100 mg benralizumab groups, respectively, reduced by 11%, 68%, 82% and 79% from the baseline levels.

A reduction in blood eosinophil counts was observed 24 hours post dosing in a Phase 2 trial.

In the phase 3 exacerbation trials, SIROCCO and CALIMA, following SC administration of benralizumab at the recommended dose, blood eosinophils were reduced to a median absolute blood eosinophil count of 0 cells/mcL, which corresponds to a median reduction of 100% (see CLINICAL TRIALS). This near complete depletion of blood eosinophils was seen at the first observed time point, 4 weeks of treatment, and was sustained throughout the treatment period for both the greater than or equal to 300/mcL and less than 300/mcL baseline blood eosinophil count cohorts.

Treatment with benralizumab was also associated with reductions in blood basophils. In the Phase 2 dose-ranging trial, at 52 weeks (12 weeks after the last dose), median blood basophil counts were changed to 42, 18, 17, and 46 cells/μL in the 2 mg, 20 mg and 100 mg benralizumab and placebo groups, respectively, compared to the baseline levels 45, 52, 46, and 40 cells/μL in the 2 mg, 20 mg and 100 mg benralizumab and placebo groups.

Immunogenicity
Overall, treatment-emergent anti-drug antibody response developed in 107 out of 809 (13%) patients treated with FASENRA at the recommended dosing regimen during the 48 to 56 week treatment period. A total of 12% (94 out of 809) of patients treated with FASENRA developed neutralizing antibodies. Anti-benralizumab antibodies were associated with increased clearance of benralizumab and increased blood eosinophil levels in patients with high anti-drug antibody titers compared to antibody negative patients. No evidence of an association of anti-drug antibodies with efficacy or safety was observed.

The data reflect the percentage of patients whose test results were positive for antibodies to benralizumab in specific assays. The observed incidence of antibody response is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to benralizumab with the incidence of antibodies to other products may be misleading.

10.3 Pharmacokinetics

The pharmacokinetics of benralizumab was approximately dose-proportional in patients with asthma following subcutaneous administration over a dose range of 20 to 200 mg.

Absorption: Following subcutaneous administration to patients with asthma, the absorption half-life was approximately 3.5 days. Based on population pharmacokinetic analysis, the estimated absolute bioavailability was approximately 59% and there was no clinically relevant difference in relative bioavailability in the administration to the abdomen, thigh, or arm.

Distribution: Based on population pharmacokinetic analysis, central and peripheral volume of distribution of benralizumab was 3.1 L and 2.5 L, respectively, for a 70 kg individual.

Metabolism: Benralizumab is a humanized IgG1 monoclonal antibody that is degraded by proteolytic enzymes widely distributed in the body and not restricted to hepatic tissue.

Elimination: From population pharmacokinetic analysis, benralizumab exhibited linear pharmacokinetics and no evidence of target receptor-mediated clearance pathway. The estimated systemic clearance (CL) for benralizumab was 0.29 L/d. Following subcutaneous administration, the elimination half-life was approximately 15.5 days.

Special Populations and Conditions

Pediatrics (< 18 years of age): Based on the population pharmacokinetic analysis, age did not affect benralizumab clearance.

Geriatrics (≥ 65 years of age): Based on population pharmacokinetic analysis, age did not

affect benralizumab clearance.

Race or Gender: A population pharmacokinetics analysis indicated that there was no significant effect of race and gender on benralizumab clearance.

Renal impairment: No formal clinical studies have been conducted to investigate the effect of renal impairment on benralizumab. Based on population pharmacokinetic analysis, benralizumab clearance was comparable in subjects with creatinine clearance values between 30 and 80 mL/min and patients with normal renal function. There are limited data available in subjects with creatinine clearance values less than 30 mL/min; however, benralizumab is not cleared renally.

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

11 STORAGE, STABILITY AND DISPOSAL

Store in a refrigerator (2°C - 8°C). Store the prefilled syringe in the original package in order to protect from light. Do not freeze. Discard unused drug into sharps container. Do not use this medicine after the expiry date that is stated on the label; the expiry date refers to the last day of the stated month.

12 SPECIAL HANDLING INSTRUCTIONS

Do not shake. Do not use if frozen.

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: Benralizumab

Chemical name: Immunoglobulin G1, anti-(human interleukin 5 receptor α-chain) (human-mouse monoclonal MEDI-563 heavy chain), disulfide with human-mouse monoclonal MEDI-563 α-chain, dimer

Molecular formula and molecular mass: Benralizumab is comprised of two heavy chains and two light chains with an overall molecular weight of approximately 150 kDa.

Structural formula: Benralizumab is a recombinant humanized afucosylated IgG1κ monoclonal antibody of approximately 150 kDa, including oligosaccharides. The antibody is composed of two identical heavy chains of approximately 49,400 Da each, and two identical light chains of approximately 23,500 Da each. Benralizumab has primarily N-linked biantennary complex-type oligosaccharides attached to each heavy chain at Asn-301, without fucose. The average size of the oligosaccharide moiety is approximately 1,500 Da per heavy chain.

Physicochemical properties: Benralizumab has an isoelectric point (pI) of 8.4-8.9, density of 1.071 g/mL, and an extinction coefficient (determined experimentally) of 1.43 $(mg/mL)^{-1}cm^{-1}$.

Product Characteristics

FASENRA (benralizumab injection) is a targeted, humanized monoclonal antibody (IgG1, kappa) that selectively binds to the alpha subunit of the human interleukin-5 receptor (IL-5Rα) with a low dissociation constant. Benralizumab is produced in Chinese hamster ovary cells by recombinant DNA technology.

FASENRA is a sterile, preservative-free, clear to opalescent, colourless to yellow solution for subcutaneous injection. Since FASENRA is a protein, translucent or white to off-white particles may be present in the solution. Each single-dose, single use prefilled syringe contains 30 mg benralizumab in 1 mL.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 3 Summary of patient demographics for phase 3 clinical trials in asthma

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex n (%)
D3250C00017 (SIROCCO)	Multicentre, randomized, double-blind, parallel group, placebo controlled study of the efficacy and safety of benralizumab in patients with severe, uncontrolled asthma	FASENRA 30 mg SC Placebo 2 dosing regimens: Q4W throughout the treatment period, Q4W for the first 3 doses and then Q8W thereafter. 48 weeks	Q4W: 399 Q8W: 398 Placebo: 407 Total: 1204	49 years (12-75)	Female: 796 (66%) Male: 408 (34%)
D3250C00018 (CALIMA)	Multicentre, randomized, double-blind, parallel group, placebo controlled study of the efficacy and safety of benralizumab in patients with severe, uncontrolled asthma	FASENRA 30 mg SC Placebo 2 dosing regimens: Q4W throughout the treatment period, Q4W for the first 3 doses and then Q8W thereafter 56 weeks	Q4W: 425 Q8W: 441 Placebo: 440 Total: 1306	49 years (12-75)	Female: 807 (62%) Male: 499 (38%)
D3250C00020 (ZONDA)	Multicentre, randomized, double-blind, parallel group, placebo controlled study of the efficacy and safety of benralizumab to reduce oral corticosteroid use in patients with uncontrolled asthma	FASENRA 30 mg SC Placebo 2 dosing regimens: Q4W throughout the treatment period, Q4W for the first 3 doses and then Q8W thereafter 28 weeks	Q4W: 72 Q8W: 73 Placebo: 75 Total: 220	51 years (20-75)	Female: 135 (61%) Male: 85 (39%)

SC: subcutaneous

Study demographics and trial design

FASENRA (benralizumab injection) was developed for the treatment of patients with severe asthma with an eosinophilic phenotype; therefore, the clinical development program was designed to study the ability of benralizumab to reduce the annual rate of asthma

exacerbations, improve lung function, reduce asthma symptoms, and reduce oral corticosteroid (OCS) use in patients across a wide range of baseline peripheral blood eosinophil levels.

The safety and efficacy of FASENRA as an add-on therapy in patients with uncontrolled asthma were evaluated in 3 randomized, double-blind, parallel-group, placebo-controlled clinical trials:

- Two replicate long-term exacerbation trials in adults and adolescents (12 years and older) with 48 and 56 weeks duration (SIROCCO and CALIMA, respectively); and
- One 28-week OCS reduction trial in adults (18 years and over) (ZONDA).

While two dosing regimens were studied in the three trials, the recommended dosing regimen is FASENRA administered every 4 weeks for the first 3 doses, and then every 8 weeks (Q8W) thereafter (see DOSAGE AND ADMINISTRATION). Only results from the recommended dosing regimen of FASENRA (i.e., Q8W) and placebo will be discussed.

A total of 805, 881 and 148 patients were randomized to treatment with FASENRA Q8W and placebo in SIROCCO, CALIMA and ZONDA, respectively (see Table 3). This included 84 adolescents (SIROCCO/CALIMA combined; 38 within the FASENRA Q8W arms and 46 within the placebo arms).

SIROCCO and CALIMA

The two exacerbation trials, SIROCCO and CALIMA, were 48 and 56 weeks in duration, respectively, and randomized a total of 2510 patients (adults and adolescents aged 12 years and older) with uncontrolled asthma. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months, Asthma Control Questionnaire (ACQ)-6 score of 1.5 or greater at screening, and reduced lung function at baseline [pre-bronchodilator forced expiratory volume in 1 second (FEV_1) below 80% in adults, and below 90% in adolescents] despite regular treatment with high-dose (> 500 mcg fluticasone propionate equivalent) inhaled corticosteroids (ICS) (SIROCCO) or with medium- (500 mcg fluticasone propionate equivalent) or high-dose ICS (CALIMA) and their current standard of care. Patients were stratified by geography, age, and blood eosinophils count (greater than or equal to 300 cells/mcL or less than 300 cells/mcL). Subjects were enrolled in SIROCCO and CALIMA irrespective of baseline blood eosinophils levels; however, they were stratified in a 2:1 ratio according to high- (greater than or equal to 300 cells/mcL) and low- (less than 300 cells/mcL) eosinophil stratums, respectively. The stratification was intended as a means of enriching the sample population for patients suggested most likely to respond to benralizumab, while accommodating subjects below this threshold in order to assess efficacy across a full range of baseline blood eosinophil levels.

The primary efficacy (intent-to-treat [ITT]) population consisted of patients with a baseline blood eosinophil count of greater than or equal to 300 cells/mcL who were taking high-dose ICS and LABA. Pre-specified efficacy analyses were also conducted in patients with baseline blood eosinophils of less than 300 cells/mcL; however, these analyses were considered to be supportive as they were not controlled for multiplicity. The primary endpoint for both studies was the annual asthma exacerbation rate ratio versus placebo within the primary efficacy (ITT) population. Key secondary endpoints were FEV_1 and ACQ-6.

ZONDA

For the 28-week oral corticosteroid reduction trial, a total of 220 asthma patients were enrolled who were being treated with daily OCS (7.5 to 40 mg per day) in addition to regular use of high-dose ICS and LABA with or without additional controller(s) to maintain asthma control. The trial included an 8 week run-in period during which the OCS was titrated to the minimum effective

dose without losing asthma control. Patients were required to have blood eosinophil counts greater than or equal to 150 cells/mcL and a history of at least one exacerbation in the past 12 months.

The primary endpoint was percent reduction from baseline of the final OCS dose during Weeks 24 to 28, while maintaining asthma control.

Table 4 Demographics and Baseline Characteristics of Asthma Trials including ITT population

	Total Population			High Dose ICS and ≥300 cells/mcL*	
	SIROCCO (N=1204)	**CALIMA (N=1306)**	**ZONDA (N=220)**	**SIROCCO (n=809)**	**CALIMA (n=728)**
Mean age (yr)	49	49	51	49	49
Female (%)	66	62	61	65	61
Caucasian (%)	73	84	93	71	86
Duration of asthma, median (yr)	15	16	12	14	16
Never smoked (%)	80	78	79	81	77
Mean baseline FEV_1 pre-bronchodilator (L)	1.67	1.76	1.85	1.66	1.78
Mean baseline % predicted FEV_1	57	58	60	56	58
Median number of exacerbations in previous year	2	2	2	2	2
Mean baseline ACQ-6	2.8	2.7	2.6	2.8	2.8

**Intent to treat population*

14.2 Study Results

Baseline blood eosinophils greater than or equal to 300 cells/mcL:
Exacerbations

The primary endpoint for SIROCCO and CALIMA was the rate of clinically significant asthma exacerbations in patients with baseline blood eosinophil counts of greater than or equal to 300 cells/mcL who were taking high-dose ICS and LABA. Clinically significant asthma exacerbation was defined as worsening of asthma requiring use of oral/systemic corticosteroids for at least 3 days, and/or emergency department visits requiring use of oral/systemic corticosteroids and/or hospitalization. For patients on maintenance oral corticosteroids, a clinically significant asthma exacerbation requiring oral corticosteroids was defined as a temporary increase in stable oral/systemic corticosteroids for at least 3 days or a single depo-injectable dose of corticosteroids.

In SIROCCO, 35% of patients receiving FASENRA experienced a clinically significant exacerbation compared to 51% on placebo. FASENRA significantly reduced the annual asthma

exacerbation rate compared to placebo by 51% (rate ratio: 0.49 [95% CI: 0.37, 0.64]; p<0.001) (Table 5). In CALIMA, 40% of patients receiving FASENRA experienced a clinically significant exacerbation compared to 51% on placebo. FASENRA significantly reduced the annual asthma exacerbation rate compared to placebo by 28% (rate ratio: 0.72 [95% CI: 0.54, 0.95]; p=0.019) (Table 6).

Table 5 Rate of Clinically Significant Exacerbations, SIROCCO (ITT Population) [a,b]

Treatment	Exacerbations per year			
	Rate	Difference	Rate Ratio (95% CI)[c]	p-value
Clinically significant exacerbations				
FASENRA (n=267)	0.74	-0.78	0.49 (0.37, 0.64)	<0.001
Placebo (n=267)	1.52	--	--	--
Exacerbations requiring hospitalization/emergency room visit				
FASENRA (n=267)	0.09	-0.16	0.37 (0.20, 0.67)	<0.001[d]
Placebo (n=267)	0.25	--	--	--

a. Baseline blood eosinophil counts of greater than or equal to 300 cells/mcL and taking high-dose ICS
b. Statistical analysis model: a negative binomial model including covariates treatment group, region, exacerbations in the previous year, and use of maintenance oral corticosteroids.
c. Annual Asthma Exacerbation Rate Ratio over 48 weeks.
d. p-value was not controlled for multiplicity.

Table 6 Rate of Clinically Significant Exacerbations, CALIMA (ITT Population) [a,b]

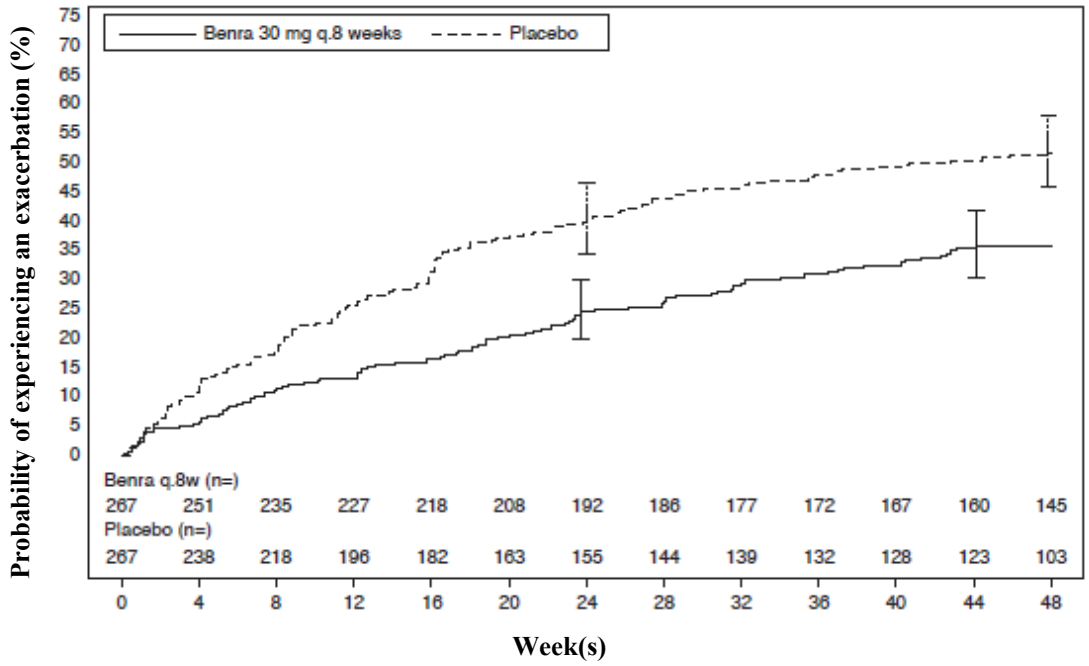
Treatment	Exacerbations per year			
	Rate	Difference	Rate Ratio (95% CI)[c]	p-value
Clinically significant exacerbations				
FASENRA (n=239)	0.73	-0.29	0.72 (0.54, 0.95)	0.019
Placebo (n=248)	1.01	--	--	--
Exacerbations requiring hospitalization/emergency room visit				
FASENRA (n=239)	0.12	0.02	1.23 (0.64, 2.35)	0.538[d]
Placebo (n=248)	0.10	--	--	--

a. Baseline blood eosinophil counts of greater than or equal to 300 cells/mcL and taking high-dose ICS
b. Statistical analysis model: a negative binomial model including covariates treatment group, region, exacerbations in the previous year, and use of maintenance oral corticosteroids.
c. Annual Asthma Exacerbation Rate Ratio over 56 weeks.
d. p-value was not controlled for multiplicity.

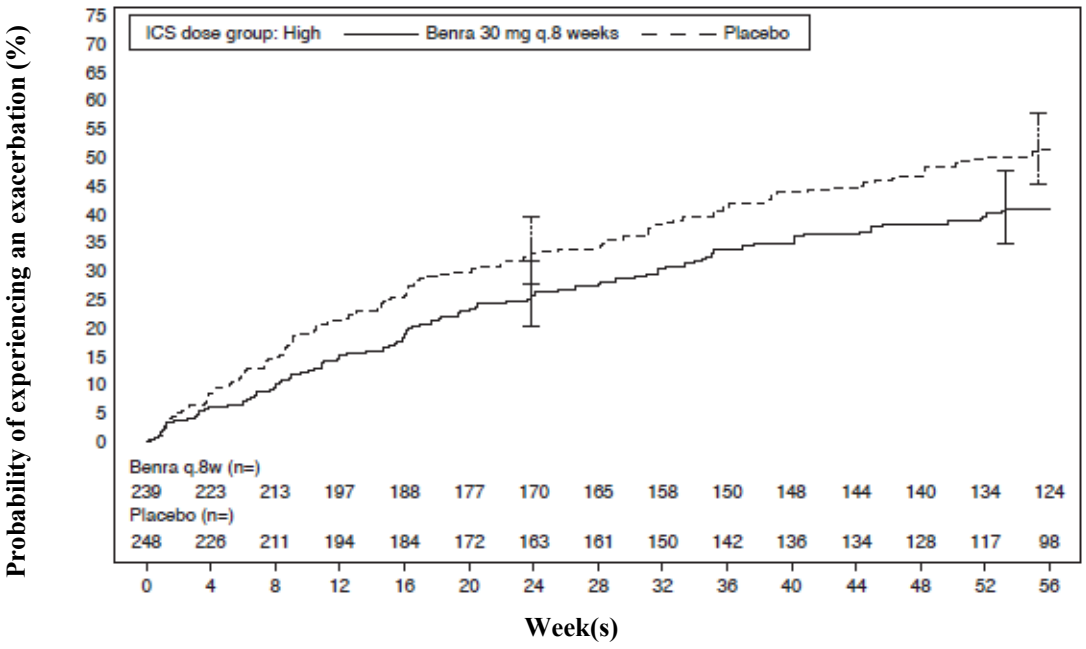
The time to first asthma exacerbation was longer for the patients receiving FASENRA compared with placebo in both trials. In SIROCCO, the risk of having an asthma exacerbation was reduced by 40% (HR [95% CI]: 0.60 [0.46, 0.78]) and in CALIMA, by 27% (HR [95% CI]: 0.73 [0.55, 0.95]) (Figure 2).

Figure 2 Kaplan-Meier Cumulative Incidence Curves for Time to First Exacerbation, SIROCCO and CALIMA

SIROCCO



CALIMA



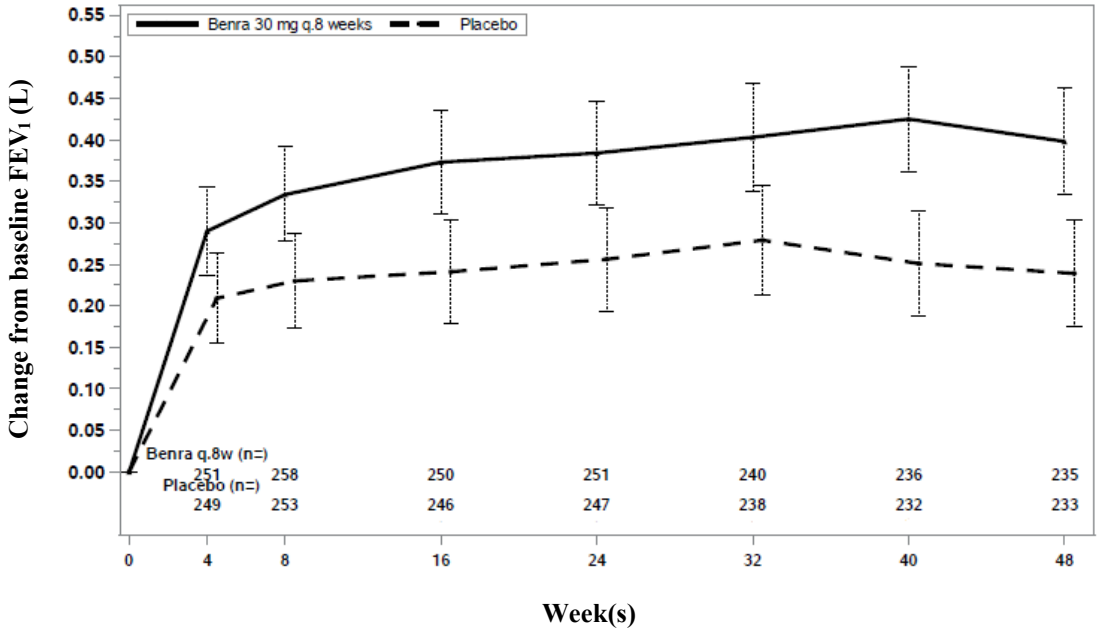
In SIROCCO, in patients with a history of 3 or more asthma exacerbations in the previous year, the annual asthma exacerbation rate from baseline to week 48 was 0.95 for FASENRA (n=103) compared to 2.23 for placebo (n=118). In CALIMA, in patients with a history of 3 or more asthma exacerbations in the previous year, the annual asthma exacerbation rate from baseline to week 56 was 0.82 for FASENRA (n=95) compared to 1.65 for placebo (n=97).

Lung Function

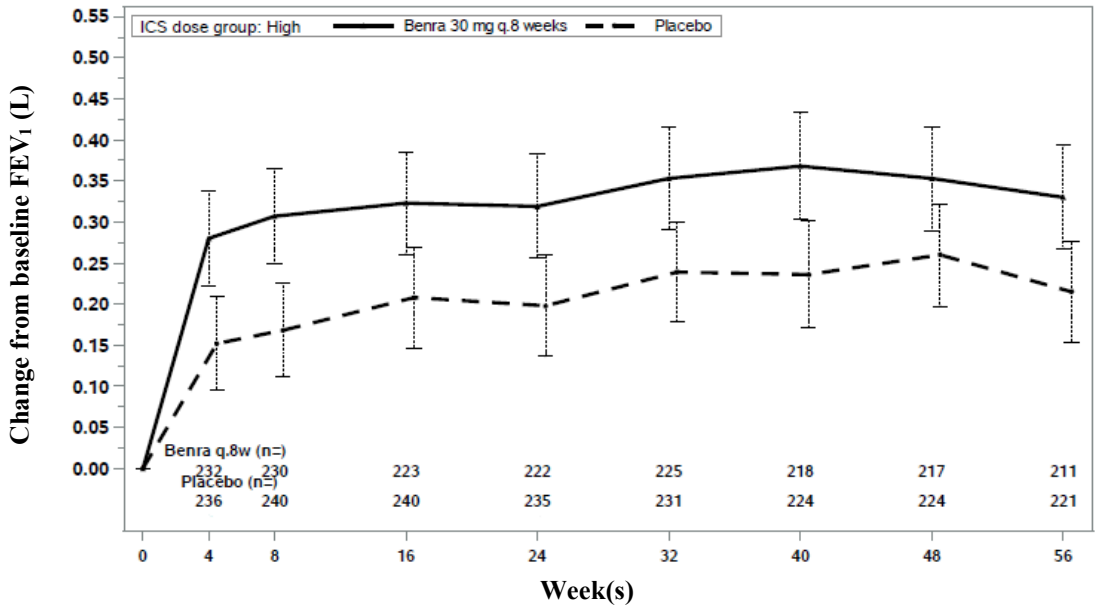
FASENRA significantly improved baseline pre-bronchodilator FEV_1 compared to placebo. In SIROCCO, the mean change from baseline in pre-bronchodilator FEV_1 was 0.159 L ([95% CI: 0.068, 0.249], p<0.001). In CALIMA, the mean change from baseline in pre-bronchodilator FEV_1 was 0.116 L ([95% CI: 0.028, 0.204], p<0.010). Compared with placebo, FASENRA provided consistent improvements over time in the mean change from baseline in FEV_1 (Figure 3).

Figure 3 Mean Change from Baseline in Pre-Bronchodilator FEV_1 (L), SIROCCO and CALIMA

SIROCCO



CALIMA



Asthma Symptoms and Quality of Life

In SIROCCO, the observed mean change from baseline to week 48 in Asthma Control Questionnaire (ACQ)-6 was -1.47 units for FASENRA compared to -1.12 units for placebo. In CALIMA, the observed mean change from baseline to week 56 was -1.49 units for FASENRA compared to -1.21 units for placebo. In SIROCCO, the observed mean change from baseline to week 48 in Standardized Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ(S)+12) was 1.56 units for FASENRA compared to 1.25 units for placebo. In CALIMA, the observed mean change from baseline to week 56 was 1.61 units for FASENRA compared to 1.32 units for placebo.

Baseline blood eosinophils less than 300 cells/mcL:

In SIROCCO, in patients with baseline blood eosinophil counts less than 300 cells/mcL, the annual asthma exacerbation rate from baseline to week 48 was 1.11 for FASENRA (n=131) compared to 1.34 for placebo (n=140) (Rate Ratio = 0.83 [95% CI: 0.59, 1.16]). In CALIMA, in patients with baseline blood eosinophil counts less than 300 cells/mcL, the annual asthma exacerbation rate from baseline to week 56 was 0.83 for FASENRA (n=125) compared to 1.38 for placebo (n=122) (Rate Ratio = 0.60 [95% CI: 0.42, 0.86]).

Oral Corticosteroid Reduction (ZONDA)

The primary endpoint in ZONDA was the percent reduction from baseline of the final OCS dose during Weeks 24 to 28, while maintaining asthma control. The median percent reduction in daily OCS dose from baseline was 75% in patients receiving recommended dose of FASENRA (95% CI: 60, 88) compared to 25% in patients receiving placebo (95% CI: 0, 33). Reductions of 50% or higher in the OCS dose were observed in 48 (66%) patients receiving FASENRA compared to 28 (37%) of those receiving placebo. The proportion of patients with a mean final dose less than or equal to 5 mg at Weeks 24 to 28 were 59% for FASENRA and 33% for placebo (odds ratio 2.74, 95% CI: 1.41, 5.31). Only patients with an optimized baseline OCS dose of 12.5 mg or less were eligible to achieve a 100% reduction in OCS dose during the study. Of those patients, 52.4% (22 of 42) receiving FASENRA and 19% (8 of 42) on placebo achieved a 100% reduction in OCS dose.

Exacerbations and time to first asthma exacerbation were also assessed as secondary endpoints. In this 28-week trial, a smaller proportion of patients receiving FASENRA (23.3%) (17 of 73) experienced ≥1 asthma exacerbation compared to placebo (52.0%) (39 of 75). A longer time to the first asthma exacerbation was also observed in patients receiving FASENRA compared to placebo.

15 NON-CLINICAL TOXICOLOGY

General Toxicology

Intravenous and subcutaneous administration to sexually mature cynomolgus monkeys for up to 9 months duration at IV doses of 10 and 25 mg/kg or at an SC dose of 30 mg/kg once every 2 weeks was associated with reductions or depletion in peripheral blood and bone marrow eosinophil counts. Reductions in eosinophil counts were an expected pharmacological effect. In addition, no adverse histopathological findings were observed in the reproductive organs of male and female monkeys. Male and female reproductive parameters (testicular volume; sperm motility, concentration, count, and morphology; reproductive hormone patterns; and menstrual cycle length) were also unaffected. Benralizumab-related adverse effects were limited to clinical signs of bruising/reddened areas around the eyes and on the face, chest, and lower abdomen (petechiae and ecchymosis), as well as decreased platelet count and indicators of circulating erythrocyte mass in one animal following intravenous dosing at 25 mg/kg body weight. No other benralizumab-related adverse effects, including on the respiratory and cardiovascular systems, were observed. The no-observed-adverse-effect level (NOAEL) was, therefore, 10 mg/kg body weight every two weeks following intravenous administration and 30 mg/kg body weight every two weeks following subcutaneous administration. The safety margins based on the intravenous and subcutaneous NOAEL values are approximately 155 and 275 times, respectively, to the maximum recommended human dose (MRHD) on an AUC basis, and 136 and 193 times, respectively, to the MRHD on a C_{max} basis.

Carcinogenicity

Long-term animal studies have not been performed to evaluate the carcinogenic potential of benralizumab.

Reproductive and Developmental Toxicology

In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was no evidence of maternal or developmental toxicity with IV administration of benralizumab throughout pregnancy and one month post-partum at maternal doses of 10 and 30 mg/kg administered every two weeks (from gestation day 20 to one month post-partum). The NOAEL was therefore the highest dose tested. The highest dose produced exposures up to approximately 319 times (on AUC basis) and 454 times (on C_{max} basis) that achieved with the MRHD. Systemic exposure to benralizumab was observed in offspring. Reduction or depletion of peripheral eosinophil counts was also observed in maternal animals and their offspring; however, the effect in infants as a result of in utero or lactational exposure is not an intended effect.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Pr FASENRA®
benralizumab injection

Read this carefully before you start taking **FASENRA** and each time you get an injection. 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 **FASENRA**.

What is FASENRA used for?
FASENRA is a prescription medicine used in addition to other asthma medicines for maintenance treatment of adult patients with severe eosinophilic asthma, whose asthma is not controlled with their current asthma medicines. Severe eosinophilic asthma is a type of asthma where patients have increased eosinophils in the blood or lungs. Eosinophils are a type of white blood cell that are associated with inflammation of the airways that can cause your asthma to get worse or can increase the number of asthma attacks.

FASENRA helps reduce the number of asthma attacks that you experience.

FASENRA is not used to treat other problems caused by eosinophils. FASENRA is not used to treat sudden breathing problems.

How does FASENRA work?
FASENRA contains the active substance, benralizumab, a monoclonal antibody that works by affecting white blood cells called eosinophils. Eosinophils are a type of white blood cell that may contribute to your asthma by causing inflammation in the lungs. By attaching to the eosinophils, FASENRA reduces the number of eosinophils in the blood and lungs.

What are the ingredients in FASENRA?
Medicinal ingredient: benralizumab
Non-medicinal ingredients: L-histidine, L-histidine hydrochloride monohydrate, α,α-trehalose dihydrate, polysorbate 20 and water.

FASENRA comes in the following dosage form:
Solution for injection.

Each single-use prefilled syringe contains 30 mg of benralizumab in 1 mL of solution.

Do not use FASENRA if:
You are allergic to benralizumab or any of the other ingredients of this medicine. Talk to your doctor about whether this may apply to you.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take FASENRA. Talk about any health conditions or problems you may have, including if you:
- have any symptoms of an allergic reaction, including to other medicines of this type (monoclonal antibodies) as they can cause severe allergic reactions when injected into the

body (see **What are possible side effects from using FASENRA?**). Serious allergic reactions have occurred in patients receiving FASENRA.
- 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. FASENRA may weaken your ability to fight certain types of parasitic infections. Parasitic infections should be treated prior to starting treatment with FASENRA.
- feel that your asthma symptoms get worse when being treated with FASENRA.

Other warnings you should know about:

Effects when treatment with FASENRA is stopped
Do not stop receiving injections of FASENRA unless advised by your doctor. Interrupting or stopping the treatment with FASENRA may cause your asthma symptoms to become worse or cause an asthma attack.

Other medicines for asthma
Do not suddenly stop taking your other asthma medications once you have started FASENRA. These medicines (especially *corticosteroids*) must be stopped gradually, under the direct supervision of your doctor.

Pregnancy and breastfeeding
- If you are pregnant, think you may be pregnant, or are planning to become pregnant, tell your doctor before using this medicine. It is preferable to avoid the use of FASENRA during pregnancy. It is not known if FASENRA may harm your unborn baby. There is a pregnancy registry for women who are treated with FASENRA while pregnant. The purpose of the registry is to collect information about the health of you and your baby. You can talk to your healthcare provider about how to take part in this registry or you can get more information and register by calling 1-877-311-8972 or by visiting http://mothertobaby.org.
- If you become pregnant while being treated with FASENRA or within 4 months of stopping treatment with FASENRA, tell your doctor right away.
- It is not known whether the ingredients of FASENRA can pass into breast milk. If you are breastfeeding or plan to breastfeed, you must tell your doctor before being treated with FASENRA.

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

How to take FASENRA:
FASENRA is given to you as an injection just under the skin (subcutaneously) by a healthcare professional who is experienced in the monitoring and treatment of signs and symptoms of allergic reactions.

Usual dose:
The recommended dose is 30 mg every 4 weeks for the first 3 injections, and then every 8 weeks thereafter.

Overdose:

If you think you have taken too much FASENRA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If a dose of FASENRA is missed, contact your healthcare professional as soon as possible to re-schedule your appointment.

What are possible side effects from using FASENRA?

FASENRA can cause side effects, although not everybody will get them.

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

Common side effects (may affect up to 1 in 10 people):

Allergic Reactions
Allergic reactions (e.g., hives, rash) have occurred in patients receiving FASENRA. These reactions often happen within minutes to hours after an injection, but sometimes symptoms can start several days later. Tell your healthcare professional and get immediate emergency medical attention if you have any of the following symptoms of an allergic reaction:

- swelling of your face, eyelids, lips, tongue, or mouth
- difficulty breathing, very wheezy, cough, chest tightness
- fainting, dizziness, feeling lightheaded (due to a drop in blood pressure)
- hives
- rash

Other common side effects that can occur with FASENRA include:

- headache
- sore throat
- fever
- injection site reactions (e.g., pain, redness, itching, swelling near where the injection was given)

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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) 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:

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date that is stated on the label. The expiry date refers to the last day of the stated month.
- Store in the original package to protect from light.
- Store in a refrigerator (2°C to 8°C). Discard unused drug if left out of the refrigerator more than 24 hours.
- Do not shake or freeze.

If you want more information about FASENRA:

- 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; 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.

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