

This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

FASENRA[®] (benralizumab)

1 NAME OF THE MEDICINE

Benralizumab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prefilled syringe contains 30 mg benralizumab in 1 mL (30 mg/mL).

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Fasenra is a clear to opalescent, colourless to yellow solution for injection in a prefilled syringe which is administered as a subcutaneous injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fasenra is indicated as add-on therapy in patients aged 12 years and over with severe eosinophilic asthma (blood eosinophil count ≥ 300 cells/ μ L or ≥ 150 cells/ μ L if on oral corticosteroid treatment) (see Section 5.1 [*Clinical Trials*]).

4.2 Dose and method of administration

Fasenra should be prescribed by a health care professional in consultation with a specialist physician experienced in the diagnosis and treatment of severe asthma. Treatment with high-dose inhaled corticosteroids (ICS) and long-acting β -agonists (LABA) should be optimised prior to commencement of treatment with Fasenra.

Adults and adolescent (12 years and over)

The recommended dose is 30 mg of Fasenra by subcutaneous injection every 4 weeks for the first 3 doses, and then every 8 weeks thereafter.

If an injection is missed on a planned date, dosing should resume as soon as possible on the indicated regime; a double dose must not be administered.

Fasenra is intended for long-term treatment. A decision to continue therapy should be made at least annually based on disease severity and level of exacerbation.

Special patient populations

Renal and hepatic impairment

No dose adjustment is required for patients with renal or hepatic impairment (see Section 5.2 [*Special patient populations/Renal impairment and Hepatic impairment*]).

Use in the elderly

No dose adjustment is required for elderly patients (see Section 5.2 [*Special patient populations/Elderly (≥65 years old)*]).

Paediatric use

The safety and efficacy of Fasenra in children below 12 years of age have not been established.

Method of administration

Fasenra is for single use in one patient only. Discard any residue.

Fasenra is administered as a subcutaneous injection by a healthcare professional, and is not for self-administration. In line with clinical practice, monitoring of patients after administration of a biological medicine is recommended (see Section 4.4 [*Hypersensitivity reactions*]).

Administer Fasenra into the upper arm, thighs or abdomen. Do not administer into areas where the skin is tender, bruised, erythematous, or hardened.

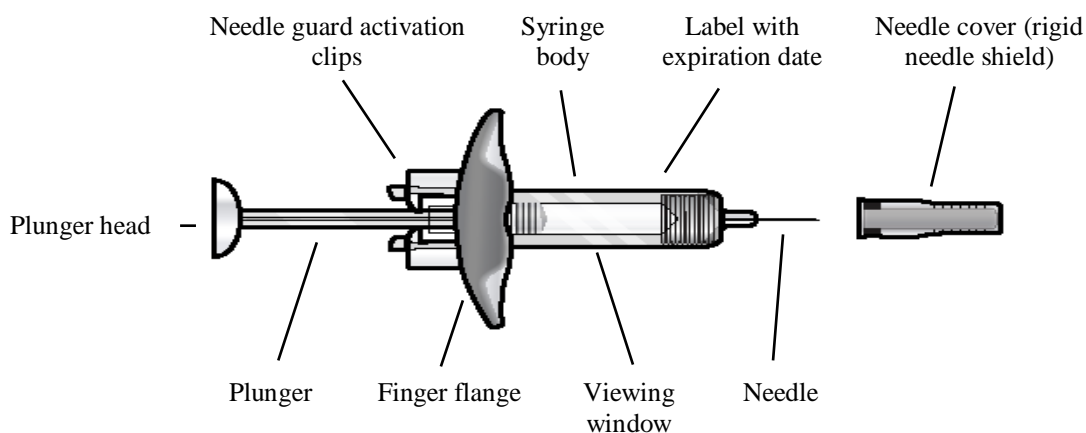
Instructions for prefilled syringe with needle safety guard

Do not shake. Do not use if frozen.

Prior to administration, allow Fasenra to reach room temperature (approximately 30 minutes). Keep Fasenra in the carton until ready to administer to protect it from light. Administer within 24 hours after taking out of the refrigerator or discard into sharps container.

See Figure 1 below to identify the prefilled syringe components for use in the administration steps.

Figure 1 Fasenra prefilled syringe



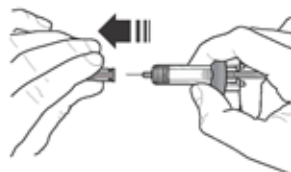
Do not touch the needle guard activation clips to prevent premature activation of the needle safety guard.

1. **Grasp the syringe body**, not the plunger, to remove prefilled syringe from the tray. Check the expiry date on the syringe.

Visually inspect Fasenra for particulate matter and discoloration prior to administration. Fasenra is clear, colourless to slightly 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 or the plunger may move. If the prefilled syringe is damaged or contaminated (eg dropped without needle cover in place), discard and use a new prefilled syringe.



3. Gently pinch the skin and insert the needle at the recommended injection site (ie upper arm, thighs or abdomen).



4. Inject all of the medication by pushing in 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.**



5. 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.**



6. Discard the used syringe into a sharps container.

4.3 Contraindications

Fasenra is contraindicated in patients who have known hypersensitivity to benralizumab or any of its excipients (see Section 4.4 [*Hypersensitivity reactions*]).

4.4 Special warnings and precautions for use

Fasenra should not be used to treat acute asthma exacerbations.

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

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

Hypersensitivity reactions

Hypersensitivity reactions (eg urticaria, urticaria papular, rash) have occurred following administration of Fasenra. These reactions generally occur within hours of administration, but in some instances have a delayed onset (ie days).

In the event of a hypersensitivity reaction, Fasenra should be discontinued.

Parasitic (helminth) infection

Eosinophils 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 Fasenra may influence a patient's response against helminth infections.

Treat patients with pre-existing helminth infections before initiating 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.

Use in the elderly

No dose adjustment is required for elderly patients (see Section 4.2 [*Special patient populations/Use in the elderly*] and Section 5.2 [*Special patient populations/ Elderly (≥65 years old)*]).

Paediatric use

The safety and efficacy of Fasenra in children below 12 years of age have not been established.

In Phase 3 studies, the treatment responses in adolescent patients (12 to 17 years of age) were less than that observed in adults, however they were not powered to detect a response in this sub-group. The adverse event profile in adolescents was generally similar to the overall population in these studies of up to 56 weeks duration. The longer term adverse effects in this age group are unknown.

Effects on laboratory tests

As expected based on the mechanism of action of benralizumab, in the pivotal Phase 3 trials, following subcutaneous administration of benralizumab at the recommended dose blood eosinophils were reduced to a median absolute blood eosinophil count of 0 cells/ μ L. This magnitude of reduction was seen at the first observed time point, 4 weeks of treatment, and was maintained throughout the treatment period. Basophils also express IL-5R α , and were also reduced.

4.5 Interactions with other medicines and other forms of interactions

No formal medicine interaction studies have been conducted.

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

An effect of benralizumab on the pharmacokinetics of co-administered medications is not expected. Based on population pharmacokinetic analysis, commonly co-administered medications had no effect on the benralizumab clearance in patients with asthma.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No fertility studies have been conducted with benralizumab in humans or animals.

Examination of surrogate fertility parameters (including organ weights and histopathology of reproductive tissues) in male and female cynomolgus monkeys treated with benralizumab at intravenous doses up to 25 mg/kg or at subcutaneous doses of up to 30 mg/kg once every 2 weeks for 9 months suggested no impairment of fertility. Systemic exposure (serum AUC) at the no adverse effect dose in monkeys was more than 400 times that in patients at the maximum recommended human dose.

Use in pregnancy – Category B1

It is preferable to avoid the use of Fasenra during pregnancy, especially during the third trimester due to the potential for eosinophil depletion in the newborn. Administration of Fasenra to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

IgG antibodies such as benralizumab are increasingly transported across the placenta as pregnancy progresses; therefore, greater fetal exposure occurs in the third trimester of pregnancy.

The effect of FASENRA on human pregnancy is unknown.

No adverse effects on pre- and postnatal survival, growth or development were observed in cynomolgus monkeys with maternal administration of intravenous doses of benralizumab (10 or 30 mg/kg) once every 2 weeks from early pregnancy (gestation day 20–22) to 1-month postpartum. Serum benralizumab levels in infants were 66% of maternal levels 7 days post-partum and declined over time (eg 10% of maternal levels 3 months post-partum). While there was no effect observed on the primary and secondary humoral immune responses to immunisation or levels of serum IgM, IgG and IgA in the offspring of the treated monkeys, there was a marked eosinophil depletion, consistent with significant placental transfer of benralizumab that resulted in pharmacologically active drug levels in infants. The immunological response to parasitic infection was not examined in the offspring.

Use in lactation

It is unknown whether benralizumab is excreted in human milk. Since antibodies can be secreted in human milk a risk to the breastfed child cannot be excluded.

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 child and the benefit of therapy for the mother.

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (Undesirable effects)

Clinical trials experience - asthma

A total of 895 patients received the recommended dose of Fasenra (30 mg every 4 weeks for the first 3 doses, and then every 8 weeks thereafter) within the 3 placebo-controlled Phase 3 clinical trials – 822 patients (including 38 adolescents) in SIROCCO and CALIMA (48 and 56-week duration respectively) and 73 patients (adults only) in a 28-week OCS sparing trial (ZONDA). Note - all 3 trials assessed 2 dosing regimens of Fasenra compared to placebo, however only the safety data for the recommended dosing regimen (Q8w; see Section 4.2) has been presented below.

In clinical trials in patients with severe asthma with eosinophilic phenotype the most commonly reported adverse drug reactions during treatment were headache and pharyngitis.

Phase 3 exacerbation trials (SIROCCO and CALIMA)

Table 1 presents the most common ($\geq 3\%$ frequency) adverse events regardless of causality from the two placebo-controlled trials (SIROCCO/CALIMA) in patients receiving the recommended dose (Q8w) of benralizumab. Table 2 presents the SIROCCO/CALIMA adverse drug reactions reported at a frequency less than 3%. All patients (including placebo) were on a background of high-dose ICS/LABA.

Table 1 The most frequent ($\geq 3\%$) adverse events regardless of causality reported during the on-treatment period and more common than placebo (SIROCCO/CALIMA - safety analyses set)

| Preferred term | Fasenra Q8w (%) (N=822) | Placebo (%) (N=847) |
|--------------------------|----------------------------|------------------------|
| Headache ^a | 8.6 | 6.3 |
| Pharyngitis ^b | 4.0 | 2.5 |
| Arthralgia | 3.9 | 2.2 |
| Cough | 3.3 | 2.1 |

^a Headache was also identified as an adverse drug reaction

^b Pharyngitis was also identified as an adverse drug reaction which was defined by the following grouped preferred terms 'Pharyngitis', 'Pharyngitis bacterial', 'Viral pharyngitis', 'Pharyngitis streptococcal' (grouped adverse drug reaction rate of 5.0% Fasenra and 3.4% placebo)

Table 2 Adverse drug reactions reported at a frequency less than 3% (SIROCCO/CALIMA - safety analyses set)

| Frequency | System Order Class | Event |
|--------------------------------------|---|--|
| Common ($\geq 1\%$ - $< 10\%$ *) | <i>Immune system disorders</i> | Hypersensitivity reactions ^a |
| | <i>General disorders & administration site conditions</i> | Pyrexia ^b ; Injection site reactions ^c |

* Definition of common, however only adverse reactions less than 3% included within this table. See above for those $\geq 3\%$

- ^a In placebo-controlled trials (SIROCCO and CALIMA), hypersensitivity reactions (defined as urticaria, urticaria papular and rash) occurred at a rate of 3.2% in both patients treated with the indicated benralizumab dose and those treated with placebo. See Section 4.4 [*Hypersensitivity reactions*]
- ^b Pyrexia was also reported as an adverse drug reaction in SIROCCO and CALIMA with a rate of 2.9% and 1.7% in patients treated with benralizumab and placebo respectively
- ^c In placebo-controlled trials (SIROCCO and CALIMA), injection site reactions (eg pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with the indicated benralizumab dose compared with 1.9% in patients treated with placebo.

Adolescents (12 to 17 years of age)

The frequency, type and severity of adverse drug reactions in the adolescent population were observed to be similar to those seen in adults.

Phase 3 OCS sparing trial (ZONDA)

In ZONDA all patients were taking daily OCS (7.5 to 40 mg per day) in addition to regular use of high-dose ICS/LABA. In general, the safety results in ZONDA were similar to those observed in SIROCCO and CALIMA.

Immunogenicity

Treatment with benralizumab, like other monoclonal antibodies, may result in an anti-drug antibody (ADA) response (see Section 5.1 [*Immunogenicity*]). However, there is no apparent correlation of ADA development to efficacy or adverse events.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems>.

4.9 Overdose

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

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

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Benralizumab is an antibody that binds to the alpha subunit of the human interleukin-5 receptor (IL-5R α) with high affinity (16 pM) and specificity. The IL-5 receptor is specifically expressed on the surface of eosinophils and basophils. The absence of fucose sugar units in the Fc domain of benralizumab results in high affinity (45.5 nM) for Fc γ RIII receptors on immune effectors cells such as natural killer (NK) cells leading to apoptosis of eosinophils and basophils through enhanced antibody-dependent cell-mediated cytotoxicity (ADCC).

Eosinophilic inflammation is an important component in the pathogenesis of asthma. Eosinophils are a rich source of proinflammatory mediators (eg eicosanoids, leukotrienes, cytokines) and granule proteins (eg eosinophil cationic protein, eosinophil peroxidase, eosinophil neurotoxin and major basic protein). Benralizumab, by enhanced ADCC, reduces eosinophilic inflammation.

Pharmacodynamic effects

The pharmacodynamic response (blood eosinophil depletion) following repeat subcutaneous dosing was evaluated in asthma patients in a 12-week Phase 2 trial. Patients with mild-moderate asthma received 1 of 3 doses of benralizumab [25 mg (n=7), 100 mg (n=6) or 200 mg (n=6) subcutaneous] or placebo (n=6) every 4 weeks for a total of 3 doses. Median blood eosinophil levels at baseline were 400, 200, 120 and 200 cells/ μ L in the 25, 100, and 200 mg benralizumab and placebo groups, respectively. Blood eosinophil depletion was observed following subcutaneous administration of benralizumab at all dose levels and no depletion was observed in the placebo group. Twenty-four hours post dosing, all benralizumab dosage groups demonstrated complete or near complete depletion of median blood eosinophil levels (0, 0 and 5 cells/ μ L respectively). There were no changes in median blood eosinophils in the placebo group. The effect on blood eosinophil depletion was maintained throughout the dosing period.

In a Phase 1 trial, the effect of benralizumab on eosinophils in airway mucosa was evaluated in asthmatic patients with 2.5% or more eosinophils in sputum. Patients received 100 or 200 mg subcutaneous benralizumab once every 4 weeks for 8 weeks (total benralizumab subcutaneous group n=9) or matching placebo (n= 5). At the end of the 12-week treatment period, there was a median reduction from baseline in eosinophils in the airway mucosa of 96% in the total benralizumab subcutaneous group compared to a 47% reduction from baseline in the placebo group which was statistically significant (p=0.039).

In the Phase 1 trial, treatment with benralizumab was also associated with reductions in blood basophils, and in both Phase 1 and 2 trials eosinophil granule products such as serum eosinophil derived neurotoxin (EDN) and eosinophil cationic protein (ECP).

In the two pivotal Phase 3 asthma trials (SIROCCO and CALIMA), following subcutaneous administration of benralizumab at the recommended dose blood eosinophils were reduced to a median absolute blood eosinophil count of 0 cells/ μ L, which corresponds to a median reduction of 100% (see Section 5.1 [*Clinical trials*] below). This magnitude of reduction was seen at the first observed time point, 4 weeks of treatment, and was maintained throughout the treatment period.

Immunogenicity

Overall, treatment-emergent anti-drug antibody (ADA) response developed in 107 out of 809 (13%) of patients treated with Fasenera at the recommended dosing regimen during the 48 to 56-week treatment period. In a majority of the ADA positive patients, in vitro neutralizing antibodies were detected. Anti-benralizumab antibodies were associated with increased clearance of benralizumab and increased blood eosinophil levels in patients with high ADA 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.

Clinical trials

Severe asthma

The safety and efficacy of Fasenra as an add-on therapy in patients with severe asthma were evaluated in 3 randomised, 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 oral corticosteroid (OCS) reduction trial in adults (18 years and over (ZONDA)).

While all 3 trials assessed 2 dosing regimens compared to placebo, the recommended dosing regimen is Fasenra administered every 4 weeks for the first 3 doses, then every 8 weeks thereafter (referred herein as Q8w; see Section 4.2) as no additional benefit was observed with the more frequent dosing regimen (administered every 4 weeks). Only the results for the recommended Q8w dosing regimen have been presented below.

A total of 805, 881 and 148 patients were randomised to treatment with Fasenra Q8w and placebo in SIROCCO, CALIMA and ZONDA respectively. This included 84 adolescents (SIROCCO/CALIMA combined; 38 within the Fasenra Q8w arms and 4 within the placebo arms). See Table 3 for further details.

Table 3 Randomised patient numbers (N) for the pivotal phase III studies (Fasenra Q8w and placebo arms only)

| | SIROCCO | CALIMA | ZONDA |
|---|---------|--------|-------|
| Total randomised population* | 805 | 881 | 148 |
| Fasenra Q8w | 398 | 441 | 73 |
| Placebo | 407 | 440 | 75 |
| High dose ICS/LABA & ≥ 300 cells/ μ L eosinophil count** | 534 | 487 | - |
| Fasenra Q8w | 267 | 239 | - |
| Placebo | 267 | 248 | - |
| High dose ICS/LABA & < 300 cells/ μ L eosinophil count^ | 271 | 247 | - |
| Fasenra Q8w | 131 | 125 | - |
| Placebo | 140 | 122 | - |

ICS – inhaled corticosteroids; LABA – long acting β -agonists; *all high-dose ICS/LABA patients regardless of baseline blood eosinophil count = Full analysis set (FAS) for SIROCCO/CALIMA and ITT population for ZONDA **SIROCCO/CALIMA enriched ITT population - high dose ICS/LABA and ≥ 300 cells/ μ L baseline blood eosinophil count; ^prespecified analysis population (Note: patients aged 12–17 years could have received medium-dose or high-dose ICS).

Table 4 Key demographic and baseline characteristics of the pivotal phase III studies (ITT populations only)

| | CALIMA | | SIROCCO | | ZONDA | |
|--------------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| | Fasenra | Placebo | Fasenra | Placebo | Fasenra | Placebo |
| Mean age (years) [range] | 49.6 [12, 74] | 48.5 [12, 75] | 47.6 [12, 74] | 48.6 [12, 75] | 52.9 [27, 75] | 49.9 [21, 74] |

| | CALIMA | | SIROCCO | | ZONDA | |
|---|-----------------------|----------------------|----------------------|----------------------|-----------------------|-----------------------|
| | Fasenra | Placebo | Fasenra | Placebo | Fasenra | Placebo |
| Mean baseline eosinophil count (cells/ μ L) [range] | 621 [300, 2600] | 642 [300, 4494] | 620 [300, 3100] | 621 [300, 2690] | 509 [154, 2140] | 656 [160, 4550] |
| Mean pre-bronchodilator FEV ₁ (L) [range] | 1.8 [0.6, 3.8] | 1.8 [0.6, 3.8] | 1.7 [0.5, 3.5] | 1.7 [0.5, 3.5] | 1.8 [0.6, 3.6] | 1.9 [0.7, 3.8] |
| Mean number of exacerbations in previous year [range] | 2.7 [2, 11] | 2.8 [2, 18] | 2.8 [2, 11] | 3.1 [2, 15] | 3.1 [1, 15] | 2.5 [1, 10] |
| Mean ACQ-6 score [range] | 2.8 [0.2, 5.7] | 2.8 [0.2, 5.8] | 2.8 [0.2, 5.7] | 2.9 [0.5, 5.5] | 2.4 [0.0, 5.2] | 2.7 [0.8, 5.0] |
| Mean ICS dose (μ g) [range] | 1002.3 [250, 4750] | 929.5 [250, 3000] | 913.4 [500, 2500] | 901.6 [125, 3000] | 1191.6 [100, 3250] | 1232.3 [100, 5000] |

ICS – inhaled corticosteroids (dose converted to fluticasone propionate dry powder equivalent); FEV₁ – forced expiratory volume in 1 second

SIROCCO and CALIMA

Patients enrolled into SIROCCO and CALIMA were required to have a history of ≥ 2 asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months, an Asthma Control Questionnaire-6 (ACQ-6) score of ≥ 1.5 at screening and reduced lung function at baseline [pre-bronchodilator forced expiratory volume in 1 second (FEV₁) $< 80\%$ in adults and $< 90\%$ in adolescents] despite treatment with high-dose ICS (SIROCCO) or with medium- or high-dose ICS (CALIMA) and their current standard of care. Medium- and high-dose ICS were defined as $\geq 250 \mu\text{g}$ and $\geq 500 \mu\text{g/day}$ fluticasone propionate dry powder formulation or equivalent respectively. The medium-dose ICS arm in CALIMA was assessed as a descriptive analysis only and has not been discussed further.

Patients were stratified 2:1 according to baseline blood eosinophils count (≥ 300 or < 300 cells/ μL). The primary efficacy population (intent-to-treat (ITT)) in both studies was patients with a high-dose ICS/LABA and a baseline blood eosinophil count ≥ 300 cells/ μL . Prespecified analyses were also conducted on the high-dose ICS/LABA populations with a baseline blood eosinophil count < 300 cells/ μL (patients not included within the ITT population) and the full analysis set (FAS) for predefined eosinophil ranges. Table 3 provides a summary of the randomised patient numbers for the different analysis groups.

ITT population (high-dose ICS/LABA and baseline blood eosinophil count ≥ 300 cells/ μL)

The primary endpoint for both trials was the annual asthma exacerbation rate ratio versus placebo within the primary efficacy population (ITT). Key secondary endpoints were FEV₁ and total asthma symptom score. Other lung function, symptom control and quality of life measures were also assessed.

Demographic, key respiratory and other baseline disease characteristics were balanced across the ITT treatment groups (Fasenra Q8w and placebo) in both trials. The demographic and patient characteristics in the ITT population were generally similar to the overall population for the two treatment arms, as well as the < 300 cells/ μL subgroup.

Treatment with Fasenra Q8w significantly reduced the annual rate of exacerbations (primary endpoint) by 51% (SIROCCO) and 28% (CALIMA) compared to placebo (see Table 5). Similar

reductions were observed compared to placebo for exacerbations requiring hospitalisations only (52%) and emergency room visits only (77%) in SIROCCO. In CALIMA, there were too few events in the placebo treatment arm to draw conclusions for exacerbations requiring hospitalisation or emergency room visits.

Clinically and statistically significant improvements in lung function were also observed with a 0.159 L (SIROCCO) and 0.116 L (CALIMA) increase in pre-bronchodilator FEV₁ relative to placebo (see Table 5). Compared with placebo, Fasenra Q8w provided consistent improvements over time in the mean change from baseline in FEV₁. Benefits of Fasenra Q8w on lung function were further supported by improvements in the mean change for morning and evening peak expiratory flow (PEF) from baseline compared to placebo.

Significant improvements were also observed for total asthma symptoms score and the Asthma Control Questionnaire (ACQ-6) after treatment with Fasenra Q8w relative to placebo (see Table 5). Significant improvements in quality of life, as measured by the Standardised Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(S)+12), were also demonstrated for Fasenra Q8w compared to placebo (see Table 5).

Table 5 Overview of key efficacy results (ITT population – high-dose ICS/LABA & baseline blood eosinophils ≥ 300 cells/ μ L) – SIROCCO and CALIMA

| Fasenra Q8w vs Placebo | | | | | |
|--|----------------------|---------|--------------------------|----------------------|---------|
| SIROCCO | | | CALIMA | | |
| N(n) v N(n) | Comparison (95% CI) | p-value | N(n) v N(n) | Comparison (95% CI) | p-value |
| Primary endpoint: Annual asthma exacerbation^a rate (rate ratio)^a | | | | | |
| 267 (267) v 267 (267) | 0.49 (0.37, 0.64) | <0.001* | 239 (239) v 248 (248) | 0.72 (0.54, 0.95) | 0.019* |
| Pre-bronchodilator FEV₁ (L) change from baseline at EOT (difference in LS means)^b | | | | | |
| 264 (235) v 261 (233) | 0.159 (0.068, 0.249) | 0.001* | 238 (211) v 244 (221) | 0.116 (0.028, 0.204) | 0.010* |
| Total asthma symptom score change from baseline at EOT (difference in LS means)^c | | | | | |
| 263 (178) v 267 (180) | -0.25 (-0.45, -0.06) | 0.012* | 237 (185) v 247 (187) | -0.23 (-0.43, -0.04) | 0.019* |
| ACQ-6 score change from baseline at EOT (difference in LS means)^d | | | | | |
| 267 (263) v 267 (267) | -0.29 (-0.48, -0.10) | 0.003 | 239 (239) v 248 (247) | -0.25 (-0.44, -0.07) | 0.008 |
| Overall AQLQ(S)+12 score change from baseline at EOT (difference in LS means)^e | | | | | |
| 267 (252) v 267 (254) | 0.30 (0.10, 0.50) | 0.004 | 239 (230) v 248 (240) | 0.24 (0.04, 0.45) | 0.019 |

^aExacerbations were defined as worsening of asthma requiring use of oral/systemic corticosteroids for ≥ 3 days and/or emergency department visits requiring use of oral/systemic corticosteroids and/or hospitalization. For patients on maintenance OCS, an exacerbation requiring OCS was defined as a temporary increase in stable oral/systemic corticosteroids for at ≥ 3 days or a single depo-injectable dose of corticosteroids.

* Statistically significant under the multiple testing procedure

^a The crude placebo rate was 1.53 in SIROCCO and 1.03 in CALIMA

^b The LS mean change from baseline at EOT for placebo was 0.239 L in SIROCCO and 0.215 L in CALIMA

^c The LS mean change from baseline at EOT for placebo was -1.04 units in SIROCCO and -1.16 units in CALIMA

^d The LS mean change from baseline at EOT for placebo was -1.17 units in SIROCCO and -1.19 units in CALIMA

^e The LS mean change from baseline at EOT for placebo was 1.26 units in SIROCCO and 1.31 units in CALIMA

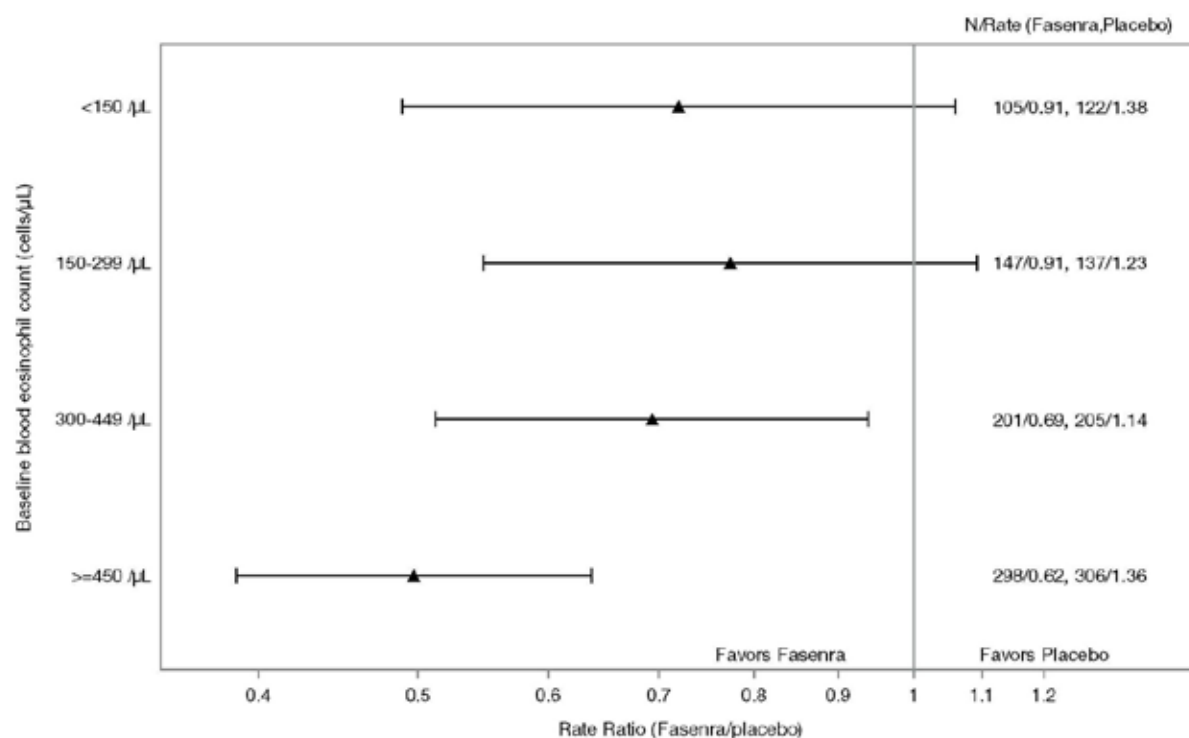
End of treatment (EOT) was Week 48 in Trial 1 and Week 56 in Trial 2.

CI Confidence interval; EOT End of treatment; FEV₁ Forced expiratory volume in 1 second; LS Least squares; N Number of patients in the analysis; n Number of patients with data at EOT.

Baseline blood eosinophil subgroup analyses

While efficacy benefits were observed with Fasenra compared to placebo irrespective of baseline eosinophil count, increasing baseline eosinophil counts were identified as a potential predictor of improved treatment response (see Figure 2).

Figure 2 Annual asthma exacerbation (primary endpoint) rate ratio comparison by baseline blood eosinophil count category, negative binomial model - forest plot (Integrated SIROCCO/CALIMA - Full analysis set, high-dose ICS)



Prior exacerbation history

A subgroup analysis on prior exacerbation history within the ITT population indicated that a higher prior exacerbation history may also be a potential predictor of an improved treatment response. When considered alone, or in combination with a higher baseline eosinophil count, these factors may further identify patients who may achieve a greater response from treatment with Fasenra.

OCS dose reduction trial (ZONDA)

ZONDA included patients who were treated with daily OCS (7.5 to 40 mg/day) in addition to regular use of high-dose ICS/LABA with or without additional controller(s) to maintain asthma control. The definition of high-dose ICS was as per SIROCCO/CALIMA. There was an 8-week run-in period during which a patient’s OCS dose was titrated to the minimum effective dose while maintaining asthma control. The baseline median OCS dose was 10 mg (range: 8-40 mg) for both treatment groups. Patients were also required to have blood eosinophil counts \geq 150 cells/ μ L and a history of at least one exacerbation in the past 12 months. All patients were included in the analysis, including 20 patients with a baseline blood eosinophil count of \geq 150-299 cells/ μ L (12 in Fasenra Q8w arm and 11 in the placebo arm).

Demographic, key respiratory and other baseline disease characteristics were balanced across the treatment groups (Fasenra Q8w and placebo).

Attachment 1: Product information AusPAR FASENRA - Benralizumab - AstraZeneca Pty Ltd - PM-2016-04636-1-5 - FINAL 21 February 2019. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>

The primary endpoint was percent (%) reduction from baseline of the final OCS dose during Weeks 24 to 28, while maintaining asthma control. Compared to placebo, patients receiving Fasenra Q8w achieved greater reductions in daily maintenance OCS dose while still maintaining asthma control. Reductions of $\geq 50\%$ in the OCS dose were observed in 66% of patients receiving Fasenra Q8w compared to 37% for the placebo arm (see Table 6). The proportion of patients with a mean final OCS dose ≤ 5 mg at Weeks 24 to 28 were 59% for Fasenra Q8w and 33% for placebo (odds ratio 2.74 (95% CI: 1.41, 5.31), $p=0.002$). Patients with an optimized baseline OCS dose (12.5 mg or less) were eligible to achieve a 100% reduction in OCS dose during the study. A significant difference was observed in the percentage of eligible patients who achieved 100% reduction with Fasenra Q8w compared to placebo (52.4% vs 19.0%; Odds ratio 4.19 (95% CI: 1.58, 11.12), $p=0.002$).

Table 6 Effect of Fasenra Q8w on OCS dose reduction - ZONDA

| | Fasenra (N=73) | Placebo (N=75) |
|---|------------------------------|-------------------|
| Wilcoxon rank sum test (primary analysis method) | | |
| Median % reduction in daily OCS dose from baseline (95% CI) | 75 (60, 88) | 25 (0, 33) |
| Wilcoxon rank sum test p-value | <0.001 | |
| Proportional odds model (sensitivity analysis) | | |
| <i>Percent reduction in OCS from baseline at Week 28</i> | | |
| $\geq 90\%$ reduction | 27 (37%) | 9 (12%) |
| $\geq 75\%$ reduction | 37 (51%) | 15 (20%) |
| $\geq 50\%$ reduction | 48 (66%) | 28 (37%) |
| >0% reduction | 58 (79%) | 40 (53%) |
| No change or no decrease in OCS | 15 (21%) | 35 (47%) |
| Odds ratio (95% CI), p-value | 4.12 (2.22, 7.63), $p<0.001$ | |

OCS – oral corticosteroids; CI – confidence intervals; N Number of patients in the analysis

Fasenra Q8W demonstrated a 70% reduction in the annual asthma exacerbation rate over 28 weeks compared with placebo (Rate ratio: 0.30 (95% CI: 0.17, 0.53), $p<0.001$), and a 93% reduction in the annual asthma exacerbation rate associated with an emergency room visit or hospitalisations (Rate ratio: 0.07 (95% CI: 0.01, 0.63), $p=0.018$) over 28 weeks compared with placebo.

Long term data

While a long-term extension study of CALIMA and SIROCCO (BORA) is ongoing, there are currently no clinical data from studies longer than CALIMA and SIROCCO (48 and 56 weeks duration respectively).

5.2 Pharmacokinetic properties

The pharmacokinetics of benralizumab were dose-proportional in patients with asthma following subcutaneous administration over a dose range of 2 to 200 mg.

Absorption

Following subcutaneous administration to patients with asthma, the absorption half-life was 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 upper 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.

Excretion

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 at 0.29 L/day. Following subcutaneous administration, the elimination half-life was approximately 15.5 days.

Special patient populations

Elderly (≥65 years old)

Based on population pharmacokinetic analysis, age did not affect benralizumab clearance.

Gender, race

A population pharmacokinetics analysis indicated that there was no significant effect of gender and race 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, mild to moderate renal impairment (eGFR 30-89 mL/min/1.73m²) did not affect benralizumab clearance. There are limited data available in patients with eGFR less than 30 mL/min/1.73m², 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.

Paediatric use

Based on the population pharmacokinetic analysis, the pharmacokinetics of benralizumab in adolescents aged 12 to 17 years was consistent with adults. Benralizumab has not been studied in children below 12 years of age (see Section 4.2 [*Special patient populations/Paediatric Use*]).

5.3 Preclinical safety data

Genotoxicity

No genotoxicity studies have been conducted. As a monoclonal antibody, benralizumab is not expected to interact with DNA or other chromosomal material.

Carcinogenicity

Long-term animal studies have not been performed to evaluate the carcinogenic potential of benralizumab. Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumour rejection. However, other reports indicate that eosinophil infiltration into tumours can promote tumour growth. Therefore, the malignancy risk in humans from an antibody that binds to IL-5R α , such as benralizumab, is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Fasenra contains the excipients histidine, histidine hydrochloride monohydrate, trehalose, polysorbate 20 and water for injections.

Fasenra does not contain latex, lactose, sucrose, gluten, tartrazine or any other azo dyes.

6.2 Incompatibilities

Incompatibilities were not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store at 2°C to 8°C (Refrigerate. Do not freeze).

Store the prefilled syringe in the original package in order to protect from light.

6.5 Nature and contents of container

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 Figure 1 above).

Fasenra is available in a pack containing one single-dose, single use, sterile prefilled syringe.

6.6 Special precautions for disposal

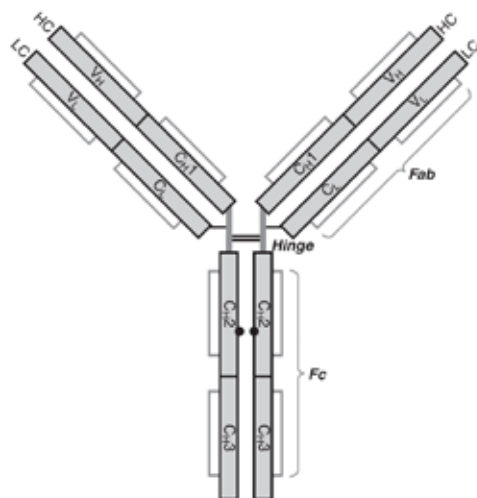
Discard used syringes into a sharps container.

In Australia, any unused medicine should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Benralizumab is a humanised, afucosylated, monoclonal antibody selective for the alpha subunit of the human interleukin-5 receptor (IL-5R α). Benralizumab is of the IgG1, kappa-class produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Benralizumab has a molecular weight of approximately 150 kDa.

Figure 3 General structure of benralizumab



CAS number: 1044511-01-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

10 DATE OF REVISION

27 March 2018

Summary table of changes

| Section changed | Summary of new information |
|-----------------|----------------------------|
| N/A | New product |

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