SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fasenra 30 mg solution for injection in pre-filled pen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 30 mg benralizumab* in 1 mL.

*Benralizumab is a humanised monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection) in pre-filled pen (Fasenra Pen)

Clear to opalescent, colourless to yellow solution and may contain translucent or white to off-white particles.

4.1 Therapeutic indications

Asthma

Fasenra is indicated as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-agonists (see section 5.1).

Eosinophilic granulomatosis with polyangiitis (EGPA)

Fasenra is indicated as an add-on treatment for adult patients with relapsing or refractory eosinophilic granulomatosis with polyangiitis (see section 5.1).

4.2 Posology and method of administration

Fasenra treatment should be initiated by a physician experienced in the diagnosis and treatment of conditions for which benralizumab is indicated (see section 4.1).

After proper training in the subcutaneous injection technique and education about signs and symptoms of hypersensitivity reactions (see section 4.4), patients with no known history of anaphylaxis or their caregivers may administer Fasenra if their physician determines that it is appropriate, with medical follow-up as necessary. Self-administration should only be considered in patients already experienced with Fasenra treatment.

Posology

Fasenra is intended for long-term treatment. A decision to continue the therapy should be made at least annually based on disease severity, level of disease control and blood eosinophil counts.

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

EGPA
The recommended dose of benralizumab is 30 mg by subcutaneous injection every 4 weeks.

Patients who develop life-threatening manifestations of EGPA should be evaluated for the need for continued therapy, as Fasenra has not been studied in this population.

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

Elderly
No dose adjustment is required for elderly patients (see section 5.2).

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

Paediatric population
The safety and efficacy of Fasenra in children and adolescents aged 6 to 17 years with asthma has not been established. Currently limited data in children 6 to 11 years old and data in adolescents aged 12 to 17 are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

The safety and efficacy of Fasenra in children less than 6 years with asthma have not been established. No data are available.

The safety and efficacy of Fasenra in children and adolescents less than 18 years with EGPA have not been established.

Method of administration

This medicinal product is administered as a subcutaneous injection.

It should be injected into the thigh or abdomen. If the healthcare professional or caregiver administers the injection, the upper arm can also be used. It should not be injected into areas where the skin is tender, bruised, erythematous, or hardened.

Comprehensive instructions for administration using the pre-filled pen are provided in the 'Instructions for Use'.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Asthma exacerbations

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.

Corticosteroids

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

Hypersensitivity reactions

Acute systemic reactions including anaphylactic reactions and hypersensitivity reactions (e.g. urticaria, papular urticaria, rash) have occurred following administration of benralizumab (see section 4.8). These reactions may occur within hours of administration, but in some instances have a delayed onset (i.e. days).

A history of anaphylaxis unrelated to benralizumab may be a risk factor for anaphylaxis following Fasenra administration (see section 4.3). In line with clinical practice, patients should be monitored for an appropriate time after administration of Fasenra.

In the event of a hypersensitivity reaction, Fasenra should be discontinued permanently and appropriate therapy should be initiated.

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 benralizumab may influence a patient's response against helminth infections.

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

Organ threatening or life-threatening EGPA

Fasenra has not been studied in patients with active organ threatening or life-threatening manifestations of EGPA (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. In a randomised, double-blind parallel-group study of 103 patients aged between 12 and 21 years with severe asthma, the humoral antibody responses induced by seasonal influenza virus vaccination do not appear to be affected by benralizumab treatment. An effect of benralizumab on the pharmacokinetics of co-administered medicinal products is not expected (see section 5.2).

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. Eosinophil depletion does not produce chronic systemic alterations of proinflammatory cytokines.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data (less than 300 pregnancy outcomes) from the use of benralizumab in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Monoclonal antibodies, such as benralizumab, are transported across the placenta linearly as pregnancy progresses; therefore, potential exposure to the fetus is likely to be greater during the second and third trimester of pregnancy.

As a precautionary measure, it is preferable to avoid the use of Fasenra during pregnancy. Its administration to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

Breast-feeding

It is unknown whether benralizumab or its metabolites are excreted in human or animal milk. A risk to the breast-fed child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from using Fasenra taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

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

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 Undesirable effects

Summary of the safety profile

The safety profile of benralizumab in asthma and EGPA are similar.

The most commonly reported adverse reactions during treatment in asthma are headache (8%) and pharyngitis (3%). The most commonly reported adverse reaction in EGPA is headache (17%). Cases of anaphylactic reaction of varied severity have been reported for benralizumab.

Tabulated list of adverse reactions

The following adverse reactions have been reported with benralizumab during clinical studies in asthma and EGPA and from post-marketing experience.
The frequency of adverse reactions is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Tabulated list of adverse reactions

MedDRA System organ class	**Adverse reaction**	**Frequency**
Infections and infestations	Pharyngitis[a]	Common
Immune system disorders	Hypersensitivity reactions[b]	Common
	Anaphylactic reaction	Not known

Nervous system disorders	Headache[c]	Common
General disorders and administration site conditions	Pyrexia Injection site reaction[d]	Common

[a] Pharyngitis was defined by the following grouped preferred terms: 'Pharyngitis', 'Pharyngitis bacterial', 'Viral pharyngitis', 'Pharyngitis streptococcal'.

[b] Hypersensitivity reactions were defined by the following grouped preferred terms: 'Urticaria', 'Papular urticaria', and 'Rash'. For examples of the associated manifestations reported and a description of the time to onset, see section 4.4.

[c] Very common in EGPA study.

[d] See 'Description of selected adverse reaction'.

Description of selected adverse reaction

Injection site reactions
In placebo-controlled asthma studies, injection site reactions (e.g. pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with the recommended benralizumab dose compared with 1.9% in patients treated with placebo. The events were transient in nature.

Long-term safety

In a 56-week extension trial (Trial 4) in patients with asthma from Trials 1, 2 and 3, 842 patients were treated with Fasenra at the recommended dose and remained in the trial. The overall safety profile was similar to the asthma trials described above. Additionally, in an open-label safety extension trial (Trial 5) in patients with asthma from previous trials, 226 patients were treated with Fasenra at the recommended dose for up to 43 months. Combined with the treatment period in previous studies, this corresponds to a median follow-up of 3.4 years (range 8.5 months – 5.3 years). The safety profile during this follow-up period was consistent with the known safety profile of Fasenra.

Paediatric population

There are limited data in paediatric patients. There were 108 adolescents aged 12 to 17 with asthma enrolled in the phase 3 trials (Trial 1: n=53, Trial 2: n=55). Of these, 46 received placebo, 40 received benralizumab every 4 weeks for 3 doses, followed by every 8 weeks thereafter, and 22 received benralizumab every 4 weeks. Adolescent patients aged 12 to 17 (n=86) from Trials 1 and 2 continued the treatment with benralizumab in Trial 4 for up to 108 weeks. The frequency, type and severity of adverse reactions in the adolescent population were observed to be similar to those seen in adults.

In an open-label, uncontrolled pharmacokinetic and pharmacodynamic study of 48 weeks duration in a limited number of paediatric patients (n=28) with uncontrolled severe asthma, the safety profile for patients aged 6 to 11 years old was similar to the adult and adolescent population (see section 4.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Doses of up to 200 mg were administered subcutaneously in clinical trials to patients with eosinophilic asthma 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.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, other systemic drugs for obstructive airway diseases, ATC code: R03DX10

Mechanism of action

Benralizumab is an anti-eosinophil, humanised afucosylated, monoclonal antibody (IgG1, kappa). It specifically binds to the alpha subunit of the human interleukin-5 receptor (IL-5Rα). The IL-5 receptor is specifically expressed on the surface of eosinophils and basophils. The absence of fucose in the Fc domain of benralizumab results in high affinity for Fc RIII receptors on immune effector cells such as natural killer (NK) cells. This leads to apoptosis of eosinophils and basophils through enhanced antibody-dependent cell-mediated cytotoxicity (ADCC), which reduces eosinophilic inflammation.

Pharmacodynamic effects

Effect on blood eosinophils
In patients with asthma, treatment with benralizumab results in near complete depletion of blood eosinophils within 24 hours following the first dose which is maintained throughout treatment. The depletion of blood eosinophils is accompanied by a reduction in serum eosinophil granule proteins (eosinophil derived neurotoxin [EDN] and eosinophil cationic protein [ECP]) and a reduction in blood basophils.

In patients with EGPA, depletion of blood eosinophils was consistent with the effect observed in asthma trials. Blood eosinophil depletion was seen at the first observed time point, 1 week of treatment, and was maintained throughout the 52-week treatment period.

Effect on eosinophils in the airway mucosa

The effect of benralizumab on eosinophils in the airway mucosa in asthmatic patients with elevated sputum eosinophil counts (at least 2.5%) was evaluated in a 12-week, phase 1, randomised, double-blind, placebo-controlled clinical study with benralizumab 100 or 200 mg administered subcutaneously. In this study, there was a median reduction from baseline in airway mucosa eosinophils of 96% in the benralizumab-treated group compared to a 47% reduction in the placebo group (p=0.039).

Clinical efficacy

Asthma

The efficacy of benralizumab was evaluated in 3 randomised, double-blind, parallel-group, placebo-controlled clinical trials between 28 to 56 weeks duration, in patients aged 12 to 75 years.

In these studies, benralizumab was administered at a dose of 30 mg once every 4 weeks for the first 3 doses, and then every 4 or 8 weeks thereafter as add-on to background treatment and was evaluated in comparison with placebo.

The two exacerbation trials, SIROCCO (Trial 1) and CALIMA (Trial 2), enrolled a total of 2 510 patients with severe uncontrolled asthma, 64% females, with a mean age of 49 years. Patients had a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment (mean of 3) in the past 12 months, Asthma Control Questionnaire-6 (ACQ-6) score of 1.5 or more at screening, and reduced lung function at baseline (mean predicted pre-bronchodilator forced expiratory volume in 1 second [FEV_1] of 57.5%), despite regular treatment with high-dose inhaled corticosteroid (ICS) (Trial 1) or with medium or high-dose ICS (Trial 2) and a long-acting β-agonist (LABA); at least one additional controller was administered to 51% and 41% of these patients, respectively.

For the oral corticosteroid (OCS) reduction trial ZONDA (Trial 3), a total of 220 asthma patients (61% female; mean age of 51 years) were enrolled; they were treated with daily OCS (8 to 40 mg per day; median of 10 mg) in addition to regular use of high-dose ICS and LABA with at least one additional controller to maintain asthma control in 53% of the cases. 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 had blood eosinophil counts ≥150 cells/μL and a history of at least one exacerbation in the past 12 months.

While 2 dose regimens were studied in Trials 1, 2, and 3, the recommended dose regimen is benralizumab administered every 4 weeks for the first 3 doses, then every 8 weeks thereafter (see section 4.2) as no additional benefit was observed by more frequent dosing. The results summarised below are those for the recommended dose regimen.

Exacerbation trials
The primary endpoint was the annual rate of clinically significant asthma exacerbations in patients with baseline blood eosinophil counts ≥300 cells/μL 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 hospitalisation. For patients on maintenance OCS, this 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 both trials, patients receiving benralizumab experienced significant reductions in annual exacerbation rates compared to placebo in patients with blood eosinophils ≥300 cells/μL. In addition, change from baseline in mean FEV_1 showed benefit as early as 4 weeks, which was maintained through to end of treatment (**Table 2**).

Reductions in exacerbation rates were observed irrespective of baseline eosinophil count; however, increasing baseline eosinophil counts was identified as a potential predictor of improved treatment response particularly for FEV_1.

Table 2. Results of annual exacerbation rate and lung function at end of treatment of Trial 1 and 2 by eosinophil count.

	Trial 1		**Trial 2**	
	Benralizumab	**Placebo**	**Benralizumab**	**Placebo**
Blood eosinophil count ≥300 cells/μL[a]	n =267	n =267	n =239	n =248
Clinically significant exacerbations				
Rate	0.74	1.52	0.73	1.01
Difference	-0.78		-0.29	
Rate ratio (95% CI)	0.49 (0.37, 0.64)		0.72 (0.54, 0.95)	
p-value	<0.001		0.019	
Pre-bronchodilator FEV_1 (L)				
Mean baseline	1.660	1.654	1.758	1.815
Improvement from baseline	0.398	0.239	0.330	0.215
Difference (95% CI)	0.159 (0.068, 0.249)		0.116 (0.028, 0.204)	
p-value	0.001		0.010	
Blood eosinophil count <300 cells/μL[b]	n =131	n =140	n =125	n =122
Clinically significant exacerbations				
Rate	1.11	1.34	0.83	1.38
Difference	-0.23		-0.55	
Rate ratio (95% CI)	0.83 (0.59, 1.16)		0.60 (0.42, 0.86)	
Pre-bronchodilator FEV_1 (L)				
Mean change	0.248	0.145	0.140	0.156
Difference (95% CI)	0.102 (-0.003, 0.208)		-0.015 (-0.127, 0.096)	

a. Intent-to-treat population (patients on high-dose ICS and blood eosinophils ≥300 cells/μL).

b. Not powered to detect a treatment difference in patients with blood eosinophils <300 cells/μL.

Across Trials 1 and 2 combined, there was a numerically greater exacerbation rate reduction and greater improvements in FEV_1 with increasing baseline blood eosinophils.

The rate of exacerbations requiring hospitalisation and/or emergency room visits for patients receiving benralizumab compared to placebo for Trial 1 were 0.09 versus 0.25 (rate ratio 0.37, 95% CI: 0.20, 0.67, p≤0.001) and for Trial 2 were 0.12 versus 0.10 (rate ratio 1.23, 95% CI: 0.64, 2.35, p=0.538). In Trial 2, there were too few events in the placebo treatment arm to draw conclusions for exacerbations requiring hospitalisation or emergency room visits.

In both Trials 1 and 2, patients receiving benralizumab experienced statistically significant reductions in asthma symptoms (Total Asthma Score) compared to patients receiving placebo. Similar improvement in favour of benralizumab was observed for the ACQ-6 and Standardised Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ(S)+12) (**Table 3**).

Table 3. Treatment difference in mean change from baseline in total asthma symptom score, ACQ-6 and AQLQ(s)+12 at end of treatment - Patients on high-dose ICS and blood eosinophils ≥300 cells/μL

	Trial 1		**Trial 2**	
	Benralizumab (n^a=267)	**Placebo** (n^a=267)	**Benralizumab** (n^a=239)	**Placebo** (n^a=248)
Total asthma symptom score[b]				
Mean baseline	2.68	2.74	2.76	2.71
Improvement from baseline	-1.30	-1.04	-1.40	-1.16
Difference (95% CI)	-0.25 (-0.45, -0.06)		-0.23 (-0.43, -0.04)	
p-value	0.012		0.019	
ACQ-6				
Mean baseline	2.81	2.90	2.80	2.75
Improvement from baseline	-1.46	-1.17	-1.44	-1.19
Difference (95% CI)	-0.29 (-0.48, -0.10)		-0.25 (-0.44, -0.07)	
AQLQ(S)+12				
Mean baseline	3.93	3.87	3.87	3.93
Improvement from baseline	1.56	1.26	1.56	1.31
Difference (95% CI)	0.30 (0.10, 0.50)		0.24 (0.04, 0.45)	

a. Number of patients (n) varies slightly due to the number of patients for whom data were available for each variable. Results shown based on last available data for each variable.

b. Asthma symptom scale: total score from 0 (least) to 6 (most); day and night time asthma symptom scores from 0 (least) to 3 (most) symptoms. Individual day and night time scores were similar.

Subgroup analyses by prior exacerbation history
Subgroup analyses from Trials 1 and 2 identified patients with higher prior exacerbation history as a potential predictor of improved treatment response. When considered alone or in combination with baseline blood eosinophils count, these factors may further identify patients who may achieve greater response from benralizumab treatment (**Table 4**).

Table 4. Exacerbation rate and pulmonary function (FEV_1) at end of treatment by number of exacerbations in the previous year - Patients on high-dose ICS and blood eosinophils ≥300 cells/µL

	Trial 1		Trial 2	
	Benralizumab (N=267)	**Placebo** (N=267)	**Benralizumab** (N=239)	**Placebo** (N=248)
Baseline of 2 exacerbations				
n	164	149	144	151
Exacerbation rate	0.57	1.04	0.63	0.62
Difference	-0.47		0.01	
Rate ratio (95% CI)	0.55 (0.37, 0.80)		1.01 (0.70, 1.46)	
Pre-bronchodilator FEV_1 mean change	0.343	0.230	0.266	0.236
Difference (95% CI)	0.113 (-0.002, 0.228)		0.029 (-0.079, 0.137)	
Baseline of 3 or more exacerbations				
n	103	118	95	97
Exacerbation rate	0.95	2.23	0.82	1.65
Difference	-1.28		-0.84	
Rate ratio (95% CI)	0.43 (0.29, 0.63)		0.49 (0.33, 0.74)	
Pre-bronchodilator FEV_1 mean change	0.486	0.251	0.440	0.174
Difference (95% CI)	0.235 (0.088, 0.382)		0.265 (0.115, 0.415)	

Oral corticosteroid dose reduction trials

ZONDA (Trial 3), a placebo-controlled study, and PONENTE (Trial 6), a single arm, open-label study, evaluated the effect of benralizumab on reducing the use of maintenance OCS.

In Trial 3, the primary endpoint was percent reduction from baseline of the final OCS dose during Weeks 24 to 28, while maintaining asthma control. **Table 5** summarises the study results for Trial 3.

Table 5. Effect of benralizumab on OCS dose reduction, Trial 3

	Benralizumab (N=73)	**Placebo (N=75)**
Wilcoxon rank sum test (primary analysis method)		

	Benralizumab (N=73)	**Placebo (N=75)**
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)		
Percent reduction in OCS from baseline at Week 28		
≥90% reduction	27 (37%)	9 (12%)
≥75% reduction	37 (51%)	15 (20%)
≥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)	4.12 (2.22, 7.63)	
Reduction in the daily OCS dose to 0 mg/day*	22 (52%)	8 (19%)
Odds ratio (95% CI)	4.19 (1.58, 11.12)	
Reduction in the daily OCS dose to ≤5 mg/day	43 (59%)	25 (33%)
Odds ratio (95% CI)	2.74 (1.41, 5.31)	
Exacerbation rate	0.54	1.83
Rate ratio (95% CI)	0.30 (0.17, 0.53)	
Exacerbation rate requiring hospitalisation/emergency room visit	0.02	0.32
Rate ratio (95% CI)	0.07 (0.01, 0.63)	

* Only patients with an optimised baseline OCS dose of 12.5 mg or less were eligible to achieve a 100% reduction in OCS dose during the study.

Lung function, asthma symptom score, ACQ-6 and AQLQ(S)+12 were also assessed in Trial 3 and showed results similar to those in Trials 1 and 2.

Trial 6 enrolled 598 adult patients with severe asthma (blood eosinophil count ≥150 cells/μL at entry or ≥300 cells/μL in the past 12 months if study entry count was <150 cells/μL) who were oral corticosteroid-dependent. The primary endpoints were proportion of patients who eliminated OCS while maintaining asthma control and proportion of patients who achieved a final OCS dose less than or equal to 5 mg while maintaining asthma control and taking into account adrenal function. The proportion of patients who eliminated maintenance OCS was 62.9%. The proportion of patients who achieved an OCS dose less than or equal to 5 mg (while maintaining asthma control and not limited by adrenal function) was 81.9%. Effects on OCS reduction were similar irrespective of blood eosinophil count at study entry (including patients with blood eosinophils <150 cells/μL) and maintained over an additional period of 24 to 32 weeks. The annualised exacerbation rate in Trial 6 was comparable to that reported in previous trials.

Long-term extension trials
The long-term efficacy and safety of benralizumab was evaluated in a phase 3, 56-week extension trial BORA (Trial 4). The trial enrolled 2123 patients, 2037 adults and 86 adolescent patients (aged 12 years and older) from Trials 1, 2 and 3. Trial 4 assessed the long-term effect of benralizumab on annual exacerbation rate, lung function, ACQ-6, AQLQ(S)+12 and maintenance of OCS reduction at the 2 dose regimens studied in the predecessor studies.

At the recommended dose regimen, the reduction in annual rate of exacerbations observed in the placebo-controlled predecessor Trials 1 and 2 (in patients with baseline blood eosinophil counts ≥300 cells/μL who were taking high-dose ICS) was maintained over the second year of treatment (**Table 6**). In patients who received benralizumab in predecessor Trials 1 and 2, 73% were exacerbation-free in the extension Trial 4.

Table 6. Exacerbations over an extended treatment period[a]

	Placebo[b] (N=338)	**Benralizumab** (N=318)		
	Trial 1 & 2	**Trial 1 & 2**	**Trial 4**	**Trial 1, 2 & 4[c]**
Rate	1.23	0.65	0.48	0.56

a. Patients that entered Trial 4 from predecessor Trials 1 and 2 with baseline blood eosinophil counts ≥300 cells/μL who were taking high-dose ICS.

b. Placebo patients in Trials 1 and 2 are included up to the end of the predecessor trial (Week 48 in Trial 1, Week 56 in Trial 2).

c. Total duration of treatment: 104 - 112 weeks

Similar maintenance of effect was observed throughout Trial 4 in lung function, ACQ-6 and AQLQ(S)+12 (**Table 7**).

Table 7. Change from baseline for lung function, ACQ-6, and AQLQ(S)+12[a]

	Trial 1 & 2 Baseline[b]	Trial 1 & 2 EOT[c]	Trial 4 EOT[d]
Pre-bronchodilator FEV_1 (L)			
n	318	305	290
Mean baseline (SD)	1.741 (0.621)	--	--
Change from baseline (SD) [e]	--	0.343 (0.507)	0.404 (0.555)
ACQ-6			
n	318	315	296
Mean baseline (SD)	2.74 (0.90)	--	--
Change from baseline (SD) [e]	--	-1.44 (1.13)	-1.47 (1.05)
AQLQ(S)+12			
n	307	306	287
Mean baseline (SD)	3.90 (0.99)	--	--
Change from baseline (SD) [e]	--	1.58 (1.23)	1.61 (1.21)

n= number of patients with data at timepoint. SD = standard deviation

a. Baseline blood eosinophil counts ≥300 cells/μL and taking high-dose ICS: benralizumab administered at the recommended dose regimen.

b. Integrated analysis of Trial 1 and 2 baseline includes adults and adolescents.

c. Integrated analysis at End of Treatment (EOT) of Trial 1 (Week 48) and Trial 2 (Week 56).

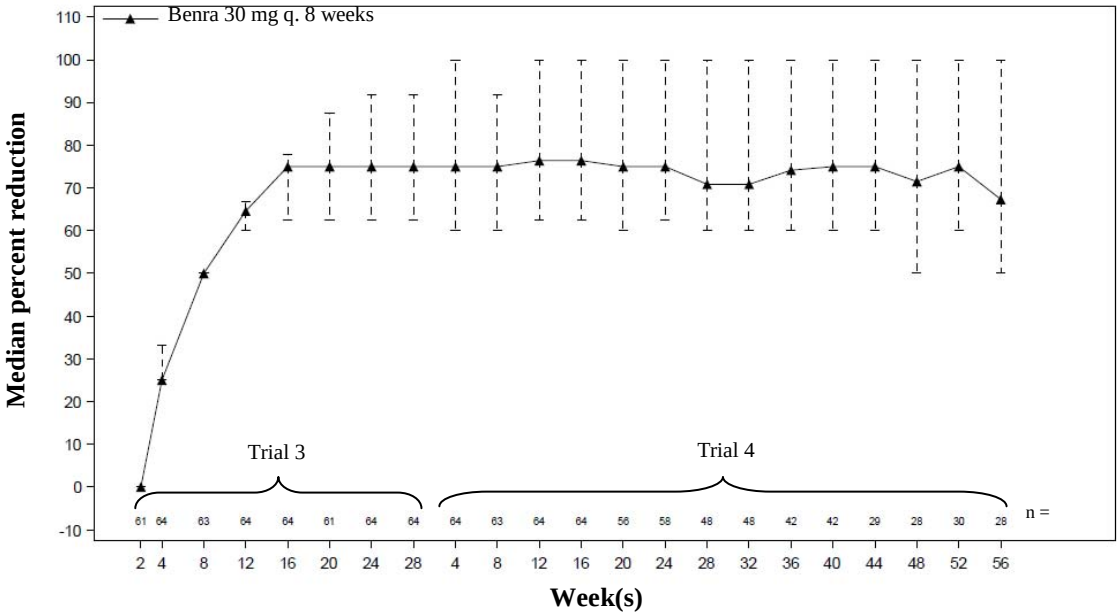
d. EOT for Trial 4 was Week 48 (the last timepoint for adults and adolescent data).

e. Baseline is prior to benralizumab treatment in Trial 1 and 2.

Efficacy in Trial 4 was also evaluated in patients with baseline blood eosinophil counts <300 cells/μL and was consistent with Trials 1 and 2.

Maintenance of the reduction in daily OCS dose was also observed over the extension trial in patients enrolled from Trial 3 (**Figure 1**).

Figure 1. Median percent reductions in daily OCS over time (Trial 3 and 4)[a]



a. Predecessor Trial 3 patients who continued benralizumab treatment into Trial 4. Patients were permitted to enter a second extension trial after a minimum of 8 weeks in Trial 4 without completing the 56-week extension period.

In Trial 5, a second long-term safety extension study (see section 4.8), the annualised exacerbation rate (0.47) in patients receiving the approved dose regimen was comparable to that reported in the predecessor Trials 1, 2 (0.65) and 4 (0.48).

Eosinophilic granulomatosis with polyangiitis (EGPA)

The efficacy of benralizumab was evaluated in a randomised, double-blind, active-controlled, non-inferiority clinical trial of 52-weeks treatment duration, in patients aged 18 years and older with EGPA. A total of 140 patients were randomised to receive either 30 mg of benralizumab or 300 mg of mepolizumab administered subcutaneously every 4 weeks. Patients enrolled had a history of relapsing or refractory disease and were on stable OCS therapy (OCS; ≥7.5 to ≤50 mg/day prednisolone/prednisone), with or without stable immunosuppressant therapy (excluding cyclophosphamide). The median baseline OCS daily dose was 10 mg and 36% were receiving immunosuppressive therapy. The OCS dose was tapered at the discretion of the investigator. Patients with active organ threatening or life-threatening EGPA were excluded from the trial.

Remission
The primary endpoint was the proportion of subjects in remission, defined as Birmingham Vasculitis Activity Score (BVAS)=0 (no active vasculitis) plus prednisolone/prednisone dose ≤4 mg/day, at both Week 36 and Week 48. As shown in Table 8, benralizumab demonstrated non-inferiority to mepolizumab for the primary endpoint. Results for accrued duration of remission and the components of remission are also shown in Table 8.

Table 8. Remission and components of remission in EGPA

	Remission (OCS≤4 mg/day + BVAS=0)		OCS≤4 mg/day		BVAS=0	
	Benra[a] N=70	Mepo[b] N=70	Benra[a] N=70	Mepo[b] N=70	Benra[a] N=70	Mepo[b] N=70
Patients in remission at both Weeks 36 and 48						
Patients, n (%)[c]	40 (58)	40 (57)	42 (61)	41 (58)	58 (83)	59 (84)
Differences in remission rate (%)[c] (95% CI) (p-value)	1.21 (-14.12, 16.53) (0.88)[d]		2.64 (-12.67, 17.95) (0.74)[d e]		-1.17 (-13.27, 10.94) (0.85)[d e]	
Accrued duration over 52 weeks, n (%)						
0 weeks[f]	9 (13)	15 (21)	9 (13)	12 (17)	0	0
>0 to <12 weeks	13 (19)	10 (14)	11 (16)	12 (17)	0	2 (3)
12 to <24 weeks	8 (11)	8 (11)	9 (13)	8 (11)	2 (3)	2 (3)
24 to <36 weeks	20 (29)	19 (27)	19 (27)	18 (26)	6 (9)	7 (10)
≥36 weeks	20 (29)	18 (26)	22 (31)	20 (29)	62 (89)	59 (84)

N=number of patients in analysis.

a. Benralizumab (Benra) 30 mg administered every 4 weeks.
b. Mepolizumab (Mepo) 300 mg administered every 4 weeks.
c. Model adjusted percentages.
d. Used for superiority testing.
e. Not formally tested in a pre-specified multiplicity testing procedure.
f. Did not achieve remission at any point.

The proportion of patients achieving remission within the first 24 weeks of treatment and remaining in remission through Week 52 was 42% for benralizumab and 37% for mepolizumab (difference in responder rate 5.54%, 95% CI: -9.30, 20.37, nominal p-value 0.46).

Using an alternative remission definition of BVAS=0 plus prednisolone/prednisone ≤7.5 mg/day, a consistent efficacy between groups for these endpoints was observed.

Patients achieved the primary remission endpoint across the prespecified demographic and baseline characteristic subgroups.

Relapse

The hazard ratio for time to first relapse (vasculitis, asthma, or sino-nasal) was 0.98 (95% CI: 0.53, 1.82, nominal p-value 0.95). Relapse was observed in 30% of patients on benralizumab and 30% of patients on mepolizumab. The annualised relapse rate was 0.50 for patients receiving benralizumab versus 0.49 for patients receiving mepolizumab (rate ratio 1.03, 95% CI: 0.56, 1.90, nominal p-value 0.93). The types of relapse were consistent for patients receiving benralizumab or mepolizumab.

Oral corticosteroids
The average daily OCS dose during Weeks 48 to 52 is presented in Table 9. A 100% reduction in the OCS dose was observed in 41% of patients receiving benralizumab compared to 26% of those receiving mepolizumab (difference 15.69%, 95% CI: 0.67, 30.71, nominal p-value 0.04).

Table 9. Average daily oral corticosteroid dose during weeks 48 to 52 in EGPA

	Number (%) of Patients	
	Benralizumab[a] (N=70)	**Mepolizumab[b] (N=70)**
0 mg	29 (41)	19 (27)
>0 to ≤4.0 mg	19 (27)	30 (43)
>4.0 to ≤7.5 mg	15 (21)	13 (19)
>7.5 mg	7 (10)	8 (11)

N=number of patients in analysis.
a. Benralizumab 30 mg administered every 4 weeks.
b. Mepolizumab 300 mg administered every 4 weeks.

Asthma Control Questionnaire-6 (ACQ-6)
The ACQ-6 mean change from baseline was -0.57 for benralizumab versus -0.61 for mepolizumab (difference 0.05, 95% CI: -0.18, 0.27, nominal p-value 0.67).

Immunogenicity

Overall, treatment-emergent anti-drug antibody (ADA) response developed in 107 out of 809 (13%) patients with asthma treated with benralizumab at the recommended dose regimen during the 48 to 56 week treatment period of the phase 3 placebo-controlled exacerbation trials. Most antibodies were neutralising and persistent. Anti-benralizumab antibodies were associated with increased clearance of benralizumab and increased blood eosinophil levels in patients with ADA titres compared to antibody negative patients; in rare cases, blood eosinophil levels returned to pre-treatment levels. Based on current patient follow-up, no evidence of an association of ADA with efficacy or safety was observed.

Following a second year of treatment of these patients with asthma from the phase 3 placebo-controlled trials, an additional 18 out of 510 (4%) had newly developed treatment-emergent antibodies. Overall, in patients who were ADA positive in the predecessor trials, titres remained stable or declined in the second year of treatment. No evidence of an association of ADA with efficacy or safety was observed.

In patients with EGPA, treatment-emergent ADA response developed in 6 out of 67 (9%) patients treated with benralizumab during the Phase 3 active-controlled 52-week treatment period. Neutralising antibody activity was detected in one of the ADA positive patients.

Paediatric population

Asthma

There were 108 adolescents aged 12 to 17 with asthma enrolled in the phase 3 trials (Trial 1: n=53, Trial 2: n=55). Of these, 46 received placebo, 40 received benralizumab every 4 weeks for 3 doses, followed by every 8 weeks thereafter, and 22 received benralizumab every 4 weeks. In these trials, the asthma exacerbation rate in adolescent patients treated with benralizumab administered at the recommended dose regimen was 0.70 (n=40, 95% CI: 0.42, 1.18) compared to 0.41 for placebo (n=46, 95% CI: 0.23, 0.73) [rate ratio 1.70, 95% CI: 0.78, 3.69].

Adolescent patients aged 12 to 17 (n=86) from Trials 1 and 2 continued treatment with benralizumab in Trial 4 for up to 108 weeks. Efficacy and safety were consistent with the predecessor trials.

In an open-label, uncontrolled pharmacokinetic and pharmacodynamic study of 48 weeks duration in a limited number of patients 6 to 11 years (n=28) with uncontrolled severe asthma, the magnitude of blood eosinophil depletion was similar to adults and adolescents.

No conclusion can be drawn regarding asthma efficacy in the paediatric population (see section 4.2).

The licensing authority has deferred the obligation to submit the results of studies with benralizumab in one or more subsets of the paediatric population in asthma (see section 4.2 for information on paediatric use).

Eosinophilic granulomatosis with polyangiitis (EGPA)

The European Medicines Agency has deferred the obligation to submit the results of studies with benralizumab in one or more subsets of the paediatric population in EGPA (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetic properties of benralizumab below are based on the population pharmacokinetics analyses from the asthma trials. 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.

Biotransformation

Benralizumab is a humanised 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 at 0.29 L/d. In patients with EGPA, the model estimated systemic clearance was 0.22 L/d. Following subcutaneous administration, the elimination half-life was approximately 15.5 days.

Special populations

Elderly (≥65 years old)
Based on population pharmacokinetic analysis, age did not affect benralizumab clearance. However, no data are available in patients over 75 years of age.

Paediatric population
Based on population pharmacokinetic analysis and clinical study data, the pharmacokinetics of benralizumab in children and adolescents aged 6 to 17 years with asthma were consistent with adults after accounting for bodyweight as applicable (see section 4.2).

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, 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.

Interaction

Based on the population pharmacokinetic analysis, commonly co-administered medicinal products (montelukast, paracetamol, proton pump inhibitors, macrolides and theophylline/aminophylline) had no effect on benralizumab clearance in patients with asthma.

5.3 Preclinical safety data

As benralizumab is a monoclonal antibody, no genotoxicity or carcinogenicity studies have been conducted.

Animal toxicology and/or pharmacology

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology or repeated dose toxicity studies in monkeys. Intravenous and subcutaneous administration to cynomolgus monkeys was associated with reductions in peripheral blood and bone marrow eosinophil counts, with no toxicological findings.

Pregnancy

In a prenatal and postnatal development study in pregnant cynomolgus monkeys, there were no benralizumab-related maternal, embryo-foetal, or postnatal effects observed.

Fertility

No dedicated animal studies have been conducted. No benralizumab-related impairment was observed in reproductive parameters of male and female cynomolgus monkeys. Examination of surrogate fertility parameters (including organ weights and histopathology of reproductive tissues) in animals treated with benralizumab suggested no impairment of fertility. However, in the offspring of monkeys dosed while pregnant, there was a reduction in eosinophils.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Trehalose dihydrate
Polysorbate 20 (E 432)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C).
Fasenra may be kept at room temperature up to 25 °C for a maximum of 14 days.
After removal from the refrigerator, Fasenra must be used within 14 days or discarded.
Store in the original package in order to protect from light.

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

6.5 Nature and contents of container

One mL solution in a sterile, single use pre-filled pen made from type I glass with staked 29-gauge ½-inch (12.7 mm) stainless steel needle, rigid needle shield, and Fluorotec-coated stopper in a pre-filled pen.

Pack containing 1 pre-filled pen.

Not all presentations may be marketed.

6.6 Special precautions for disposal

Prior to administration, allow the pre-filled pen to reach room temperature 20 °C to 25 °C by leaving the carton out of the refrigerator for around 30 minutes.

Visually inspect Fasenra for particulate matter and 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.

Additional information and instructions for the preparation and administration of Fasenra using the pre-filled pen are given in the package leaflet and ‘Instructions for Use’.

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

7. MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited,
1 Francis Crick Avenue,
Cambridge,
CB2 0AA,
UK.

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