SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fasenra 30 mg solution for injection in pre-filled syringe
Fasenra 30 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pre-filled syringe
Each pre-filled syringe contains 30 mg benralizumab* in 1 ml.

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

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Fasenra treatment should be initiated by a physician experienced in the diagnosis and treatment of severe asthma.
After proper training in the subcutaneous injection technique and education about signs and symptoms of hypersensitivity reactions, 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

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. 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.

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 exacerbation control and blood eosinophil counts.

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

Fasenra is not indicated for children.

Method of administration

Fasenra 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 syringe/pre-filled pen (Fasenra 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

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.

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

Patients with pre-existing helminth infections should be treated 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.

4.5 Interaction with other medicinal products and other forms of interaction

In a randomized, 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 a fetus is likely to be greater during the second and third trimester of pregnancy.

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. Risk to the breastfed 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 most commonly reported adverse reactions during treatment are headache (8%) and pharyngitis (3%). Anaphylactic reactions have been reported.

Tabulated list of adverse reactions

A total of 2,514 patients, out of whom 1,663 patients had severe uncontrolled eosinophilic asthma, received benralizumab during clinical studies of 48 to 56 weeks duration.

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

Table 1. Tabulated List of Adverse Reactions

System Organ Class	Adverse Reaction	Frequency
Infections & infestations	Pharyngitis*	Common
Immune system disorders	Hypersensitivity reactions** Anaphylactic reaction	Common Not known
Nervous system disorders	Headache	Common
General disorders and administration site conditions	Pyrexia Injection site reaction	Common

* Pharyngitis was defined by the following grouped preferred terms: ‘Pharyngitis’, ‘Pharyngitis bacterial’, ‘Viral pharyngitis’, ‘Pharyngitis streptococcal’.

** 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.

Description of selected adverse reaction

Injection site reactions

In placebo-controlled 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.

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 adverse event 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 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.

Reporting of suspected adverse events

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose

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. PHARMACOLOGICAL PROPERTIES

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 binds to the alpha subunit of the human interleukin-5 receptor (IL-5Rα) with high

affinity and specificity. 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 FcγRIII 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

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.

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, doubleblind, placebo-controlled clinical study with benralizumab 100 or 200 mg SC. 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

The efficacy of Fasenra 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, Fasenra 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, 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 [FEV1] 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 dosing regimens were studied in Trials 1, 2, and 3, the recommended dosing regimen is Fasenra 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 dosing 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 Fasenra 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	
	Fasenra	Placebo	Fasenra	Placebo
Blood eosinophil count ≥300 cells/μLa	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 FEV1 (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/μLb	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 FEV1 (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/L).

[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 FEV1 with increasing baseline blood eosinophils. The rate of exacerbations requiring hospitalisation and/or emergency room visits for patients receiving Fasenra 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 Fasenra experienced statistically significant reductions in asthma symptoms (Total Asthma Score) compared to patients receiving placebo. Similar improvement in favour of Fasenra was observed for the Asthma Control Questionnaire-6 (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	
	Fasenra (n^a=267)	Placebo (n^a=267)	Fasenra (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 (FEV1) 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	
	Fasenra (N=267)	**Placebo** (N=267)	**Fasenra** (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 FEV1 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 FEV1 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 Fasenra 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** summarizes the study results for Trial 3.

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

	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)		
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 annualized exacerbation rate in Trial 6 was comparable to that reported in previous trials.

Long-term extension trials

The long-term efficacy and safety of Fasenra 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 Fasenra on annual exacerbation rate, lung function, ACQ-6, AQLQ(S)+12 and maintenance of OCS reduction at the 2 dosing regimens studied in the predecessor studies.

At the recommended dosing 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 Fasenra 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)	Fasenra (N=318)		
	Trial1&2	Trial1&2	Trial4	Trial1,2&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]

	Trial1&2 Baseline[b]	Trial1&2 EOT[c]	Trial4 EOT[d]
Pre-bronchodilator FEV1 (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: Fasenra administered at the recommended dosage 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).

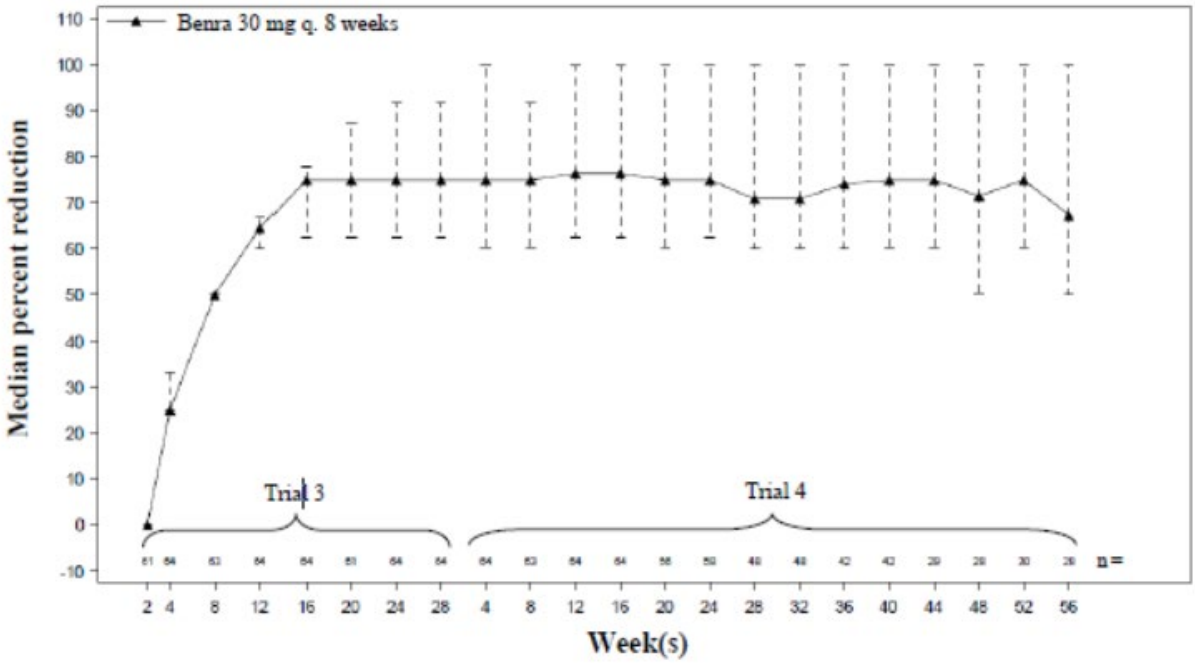
d. EOT for Trial 4 was Week 48 (the last timepoint for adults and adolescent data).

e. Baseline is prior to Fasenra 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 Fasenra 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 dosing regimen was comparable to that reported in the predecessor Trials 1, 2 (0.65) and 4 (0.48).

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 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 high anti-drug antibody 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 anti-drug antibodies with efficacy or safety was observed.

Following a second year of treatment of these patients 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 anti-drug antibody positive in the predecessor trials, titres remained stable or declined in the second year of treatment. No evidence of an association of anti-drug antibodies with efficacy or safety was observed.

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.

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. Following subcutaneous administration, the elimination half-life was approximately 15.5 days.

Special populations

Elderly patients (≥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.

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.

Drug-Drug Interaction

An effect of benralizumab on the pharmacokinetics of co-administered medicinal products is not expected. 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

Water for Injection
α,α-trehalose dihydrate
L-histidine hydrochloride monohydrate

L-histidine
polysorbate 20

6.2 Incompatibilities

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

6.3 Shelf life

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

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 the pre-filled syringe/pre-filled pen 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

Pre-filled syringe
One mL solution in a single-use pre-filled syringe made from type I glass with a staked 29-gauge ½-inch special thin wall needle, rigid needle shield, with an elastomeric plunger stopper.
Pack containing 1 single-use pre-filled syringe.
Pre-filled pen
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 single-use pre-filled pen.

6.6 Special precautions for disposal and other handling

Fasenra solution for injection is supplied in a sterile single-use pre-filled syringe or pre-filled pen for individual use. Do not shake. Do not freeze.
Prior to administration, warm Fasenra by leaving carton at room temperature. This generally takes 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 syringe or pre-filled pen (Fasenra Pen) are given in the package leaflet and 'Instructions for Use'.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Manufacturer

Catalent Indiana LLC, 1300 South Patterson Drive, Bloomington, IN 47403, USA

8. License holder and Importer

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