Taiwan Food and Drug Administration

Assessment Report

Trade Name：肺昇朗注射液劑 30 毫克 /
FASENRA solution for injection 30mg

Active Ingredient：Benralizumab

License Number：MOHW-BI 001101

Applicant：臺灣阿斯特捷利康股份有限公司

Approval Date：2019/03/15

Indication：

FASENRA 適用於嗜酸性白血球表現型的嚴重氣喘成人患者，做為附加維持治療。

FASENRA is indicated for the add-on maintenance treatment of adult patients with severe asthma and with an eosinophilic type.

1. Background Information

Trade Name	肺昇朗注射液劑 30 毫克 / FASENRA solution for injection 30mg
Active Ingredient(s)	Benralizumab
Applicant	臺灣阿斯特捷利康股份有限公司
Dosage Form & Strengths	Solution for Injection 30mg
Indication	FASENRA 適用於嗜酸性白血球表現型的嚴重氣喘成人病人，做為附加維持治療。 FASENRA is indicated for the add-on maintenance treatment of adult patients with severe asthma and with an eosinophilic type.
Posology	前 3 劑為每 4 週一次皮下注射 30 毫克，之後每 8 週一次。 Administer by subcutaneous injection. Recommended dose is 30 mg every 4 weeks for the first 3 doses, followed by once every 8weeks thereafter.
Pharmacological Category **ATC Code**	R03DX10

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Benralizumab produced in CHO cell line is a recombinant humanized IgG1κ monoclonal antibody of approximately 150 kDa, including oligosaccharides. The antibody is composed of two identical heavy chains of approximately 49,400 Da each, and two identical light chains of approximately 23,500 Da each.

The manufacturer of drug substance is AstraZeneca Pharmaceuticals LP, USA. Detailed information of generation and control of cell banks, quality of raw materials, process validation with proper in-process controls, and validation of viral clearance, are provided according to ICH Q5A, Q5B, and Q5D to demonstrate the safety and consistency. Characterization and comparative studies include primary structure, higher order structure, carbohydrate structure, charge and size heterogeneity, and biological properties. Product- and process-related impurities are properly identified and controlled. Specification, analytical methods with validation, results of batch analysis, and CoA are provided to support the quality and consistency of drug substance. Stability study is performed according to ICH Q1A (R2), Q1E and Q5C. Up to date, 24-months results of commitment lots in long-term storage condition are provided and are within predefined acceptance criteria with no significant changes. Up to 3 cycles of freeze-thaw has no impact on the quality of drug

substance.

2.1.2 Drug product

The benralizumab drug product is a sterile liquid dosage form presented in an accessorized prefilled syringe intended for subcutaneous administration. Each syringe contains 30 mg of benralizumab in a nominal 1.0 mL volume. The manufacturer of drug product is Cook Pharmica LLC, USA.

Excipients used are complied with USP/NF, Ph. Eur., and/or JP. Diagram of manufacturing process with in-process controls and process validation are properly provided. The release and shelf-life specifications include appearance, purity, quantity, safety, bioactivity and other general quality tests. Results of batch analysis are within the acceptance criteria. CoA of drug product is provided and shows satisfactory. Stability studies are conducted under long-term, accelerated, and stressed conditions. Photostability, elemental impurities and thermal cycling stability are also performed. Provided results support the shelf-life of 36 months at 5±3℃ protect from light.

In conclusion, the technical document provided is appropriate to support the quality of FASENRA solution for injection 30 mg.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

The active ingredient of FASENRA is benralizumab, which is designed to target the alpha subunit of IL-5R (IL-5Rα). In vitro pharmacological studies showed that benralizumab binds to recombinant human and monkey IL-5Rα but did not cross-react with the murine one. Based on the differential reactivity of benralizumab toward human and murine IL-5Rα, literatures have mapped the binding epitope of benralizumab on human IL5Rα and found that isoleucine 61 of human IL-5Rα is the critical residue for benralizumab binding. Benralizumab specifically bound to eosinophils, basophils and bone marrow mononuclear cells (BMMNCs) but other hematopoietic lineages. Benralizumab blocked the interaction between IL-5 and its receptor, and inhibited IL-5-dependent cell proliferation. Moreover, benralizumab triggered apoptosis of eosinophils, basophils and BMMNCs through antibody-dependent cell-mediated cytotoxicity but not complement dependent cytotoxicity. In vivo pharmacological studies demonstrated that benralizumab inhibits IL-5-induced peripheral blood eosinophilia and shows beneficial effects on allergen-induced asthma in monkey models. Safety pharmacology of benralizumab was evaluated in the repeated dose subcutaneous and intravenous toxicity studies in monkeys. No significant changes in the safety pharmacologic parameters were noted in benralizumab-treated animals up to the highest dose examined.

2.2.2 Toxicological Studies

In general toxicity studies, no significant toxicities were observed in benralizumab-treated animals up to the highest dose examined. Depletion of eosinophils was noted in most benralizumab-treated animals due to the pharmacological effects of benralizumab. Anti-drug antibodies were detected in some benralizumab-treated animals. No fertility parameters of both sexes were changed in a 39-week monkey repeated dose toxicity study. No benralizumab-related adverse effects were noted in an enhanced pre- and postnatal development study in monkeys up to the highest dose examined. No typical genotoxicity or carcinogenicity study was conducted with benralizumab. Benralizumab was considered as no or low risk on genotoxicity and carcinogenicity based on thoughtful assessments. In addition, no local toxicity at the injection site or immunotoxicity was observed. Some unexpected staining of myocytes in striated (skeletal or cardiac) muscle and mononuclear cells in spleen for either human or cynomolgus monkey were observed, but no related toxicities in toxicology studies in monkeys or information in published literature could be found.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The pharmacokinetics of benralizumab was approximately dose-proportional in patients with asthma following subcutaneous administration over a dose range of 20 to 200 mg. Based on population pharmacokinetic analysis, the estimated absolute bioavailability was approximately 58% and there was no clinically relevant difference in relative bioavailability in the administration to the abdomen, thigh, or arm.

The central and peripheral volume of distribution was 3.2 L and 2.5 L for a 70 kg individual. As a human IgG1 monoclonal antibody, benralizumab is expected to be degraded by proteolytic enzymes. The estimated typical systemic clearance for benralizumab was 0.29 L/d for a subject weighing 70 kg. Following subcutaneous administration, the elimination half-life was approximately 15 days.

2.3.2 Interaction Studies

No formal drug-drug interaction studies have been conducted. Based on the population pharmacokinetic analysis, commonly co-administered medicinal products had no effect on benralizumab clearance in patients with asthma. IL-5Rα is not expressed on hepatocytes and other than IL-5 and the eosinophil chemokines eotaxin-1 and eotaxin-2, treatment with benralizumab has no identified effect on other circulating cytokines.

Taken together, these data suggest that the potential risk of interactions between benralizumab and other drugs is low.

2.3.3 Special Populations

Age (≧12 years old), gender, renal impairment, and hepatic impairment had no significant effect on the pharmacokinetics of benralizumab based on population pharmacokinetics analysis. No pharmacokinetic data are available for pediatric patients below the age of 12 years.

The incidence of anti-benralizumab antibodies in phase 3 was about 7 to 14% and most antibodies were neutralizing and persistent. The estimate CL was increased 121% (2.21-fold with 90% CI [2.15, 2.26]) when ADA status was positive based on population PK analysis.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

In this submission, three Phase III pivotal studies were provided to support efficacy of FASENRA as an add-on maintenance treatment for severe asthma with an eosinophilic phenotype in adult patients. The key efficacy findings of these studies are summarized below.

- ***Studies [D3250C00017] ([SIROCCO]) and [D3250C00018] ([CALIMA])***

Both studies were Phase III, randomized, double-blind, multi-national, placebo-controlled study designed to evaluate the efficacy of a fixed 30 mg dose of benralizumab administered subcutaneous in patients with a history of asthma exacerbations and severe asthma. The only difference between the two studies is the study duration (48-week for [SIROCCO] and 56-week for [CALIMA]).

For both studies, the primary efficacy endpoint was annual asthma exacerbation rate, and the two key secondary efficacy endpoints were change from baseline in pre-bronchodilator FEV_1 at Week 48 and change from baseline in total asthma symptom score at Week 48. The primary efficacy population was patients in high-dose ICS patients with baseline blood eosinophil counts ≧ 300 μL.

For Study [SIROCCO], the analysis of the primary efficacy endpoint showed that both benralizumab 30 mg Q4W and Q8W dose regimens statistically significantly reduced the annual asthma exacerbation rate over 48 weeks compared with placebo by 45 % ($p < 0.001$) and 51% ($p < 0.001$), respectively. In addition, both benralizumab 30 mg Q4W and Q8W dose regimens demonstrated statistically significant improvements over placebo for change from baseline in pre-bronchodilator FEV_1 at Week 48 (both $p \leqq 0.022$). For the change in total asthma score at Week 48, a statistically significant improvement was demonstrated for benralizumab 30 mg Q8W compared with placebo ($p = 0.012$) but not for benralizumab 30 mg Q4W compared with placebo ($p = 0.442$).

For Study [CLAIMA], both benralizumab 30 mg Q4W and Q8W dose regimens statistically significantly reduced the annual asthma exacerbation rate over 56 weeks compared with placebo by 36 % ($p = 0.002$) and 28% ($p = 0.019$), respectively. In addition, both

benralizumab 30 mg Q4W and Q8W dose regimens demonstrated statistically significant improvements over placebo for change from baseline in pre-bronchodilator FEV_1 at Week 56 (0.125 L [95% CI: 0.037, 0.213] and 0.116 L [95% CI: 0.028, 0.204], respectively; both $p \leqq 0.010$). For the change in total asthma score at Week 56, a statistically significant improvement was demonstrated for benralizumab 30 mg Q8W compared with placebo ($p = 0.019$) but not for benralizumab 30 mg Q4W compared with placebo ($p = 0.224$).

- ***Study [D3250C00020] ([ZONDA]):***

Study [ZONDA] was a Phase III, randomized, double-blind, multi-national, placebo-controlled study to evaluate the efficacy of benralizumab 30 mg Q4W and Q8W in patients with severe asthma.

For the primary efficacy endpoint, both the benralizumab 30 mg Q4W and Q8W groups demonstrated a statistically significant median percent reduction from baseline in the final OCS dose at Week 28 compared with placebo using a Wilcoxon rank-sum test ($p < 0.001$ for both groups).

As a result, the Sponsor had provided sufficient evidence to support the efficacy of FASENRA (benralizumab) 30 mg Q8W as an add-on maintenance treatment for severe asthma with an eosinophilic phenotype in adult patients.

2.4.2 Safety Results

Potential risks

Potential risks of FASENRA (benralizumab) include hypersensitivity reactions, and risk of helminth (parasite) infection. In the occurrence of hypersensitivity reaction, FASENRA should be discontinued. Although there are no reports of parasite infection in the phase 3 program, patients with known parasite infections were excluded from the clinical trials. Treating patients with pre-existing parasite infection before initiation of FASNRA is recommended.

SIROCCO and CALIMA

The two phase 3 placebo-controlled studies (SIROCCO and CALIMA) from 48 or 56 weeks duration enrolled 2514 subjects, in which 1663 subjects were severe asthma with poor control. Adverse reactions that occurred at greater than or equal to 3% incidence are shown in Table 1.

Table 1. Adverse Reactions with FASANRA with Greater than or equal to 3% incidence

Adverse Reactions	FASENRA (N=822) %	Placebo (N=847) %
Headache	8	6
Pyrexia	3	2
Pharyngitis*	5	3
Hypersensitivity reactions**	3	3

* Pharyngitis was defined by the following terms: 'Pharyngitis', 'Pharyngitis bacterial', 'Viral pharyngitis', 'Pharyngitis streptococcal'.

** Hypersensitivity Reactions were defined by the following terms: 'Urticaria', 'Urticaria papular', and 'Rash'

Regarding injection site reaction TEAEs, 18 patients (2.2%) in the Q8W group, and 16 patients (1.9%) in the placebo group experienced injection site reaction.

ZONDA

Adverse reactions from ZONDA with 28 weeks of treatment with FASENRA (n = 73) or placebo (n = 75) in which the incidence was more common in FASENRA than placebo include headache (8.2% compared to 5.3%, respectively) and pyrexia (2.7% compared to 1.3%, respectively).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity for FASENRA. Overall, treatment-emergent anti-drug antibody response developed in 13% of patients treated with FASENRA at the recommended dosing regimen during the 48 to 56 week treatment period. A total of 12% of patients treated with FASENRA developed neutralizing antibodies. No evidence of an association of anti-drug antibodies with efficacy or safety was observed.

2.5 Bridging Study Evaluation

PK/PD section

Two global pivitol studies were included 205 Asian subjects (12.6% of total；Asian subjects were Japanese and Korean) in the population PK analysis. The C_{max}, C_{trough}, and AUC_t of benralizumab at the 30 mg Q8W steady state in Asian were 1.13-folds, 1.12-folds and 1.14-folds than non-Asian population.

Considering (1) the inter-subject variation of benralizumab was about 50~60% via SC route at single dose of 100 to 200 mg and (2) the metabolism pathway of benralizumab is *via*

catabolism which influenced by genetic polymorphism is limited, therefore benralizumab was shown none to minimally ethnically sensitive between Asians and non-Asians from PK reviewer's perspective.

Clinical Section

Asian population accounts for around 11% to 14% of the entire population in the two pivotal studies (SIROCCO and CALIMA). The number is over 200 subjects and most of them are East Asians.

According to the BSE package submitted by the applicant, subgroup analyses of Asian population in clinical efficacy and safety were done. In spite of several differences about demographics and baseline characteristics in Asians and non-Asians, similar benefits and safety signals were noted in Asian population compared to non-Asian population.

Based on available information, the waiver of BSE was recommended by the regulatory agency after all.

2.6 Conclusion

The NDA package of FASENRA submitted by Astrazeneca AB is considered acceptable in CMC, PT, PK/PD, Clinical and Statistical sections. The overall B/R of FASENRA (benralizumab) is thought to be positive as add on maintenance therapy in adult patients with severe eosinophilic asthma.

Approval is recommended and the recommended posology is as below:

Administer by subcutaneous injection. Recommended dose is 30 mg every 4 weeks for the first 3 doses, followed by once every 8weeks thereafter.

3. Post-Marketing Requirements

According to the applicant's words, patients who completed ZONDA study were eligible to enroll in the BORA study. Submission of CSR of BORA study once it is completed is required.