CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761070
PDUFA Goal Date	November 16, 2017
OSE RCM #	2016-2789
Reviewer Name(s)	Charlotte Jones, MD, PhD, MSPH
Team Leader	Donella Fitzgerald, Pharm.D.
Deputy Division Director	Jamie Wilkins Parker, Pharm.D.
Review Completion Date	July 27, 2017
Subject	Evaluation of Need for a REMS
Established Name	Benralizumab
Trade Name	Fasenra
Name of Applicant	AstraZeneca AB
Therapeutic Class	Humanized monoclonal antibody
Formulation(s)	30mg single dose, accessorized pre-filled syringe
Dosing Regimen	30mg subcutaneous every 4 weeks for the first three doses then every 8 weeks thereafter, administered by a healthcare professional.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity, benralizumab, is necessary to ensure the benefits outweigh its risks. AstraZeneca submitted a Biologic Licensing Application (BLA 761070) for benralizumab with the proposed indication for add-on maintenance treatment for severe asthma with an eosinophilic phenotype in adult patients 18 years of age and older. The risks associated with benralizumab include infections, malignancy, hypersensitivity events and immunogenicity. The sponsor did not submit a proposed REMS or risk management plan with this application. DRISK believes that a REMS is not needed to ensure the benefits of benralizumab outweigh its risks.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) benralizumab is necessary to ensure the benefits outweigh its risks.[a] AstraZeneca AB (AZ) submitted a New Biologic Licensing Application (BLA 761070) for benralizumab with the proposed indication for add-on maintenance treatment for severe asthma with an eosinophilic phenotype in adult patients 18 years of age and older. This application is under review in the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). The Sponsor did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Benralizumab, a NME, is a humanized afucosylated, interleukin 5-receptor alpha-directed cytolytic monoclonal antibody immunoglobulin G. The sponsor reports the high affinity binding between benralizumab and the FcγRII receptors on immune effector cells leads to apoptosis of eosinophils and basophils through antibody-dependent cell-mediated cytotoxicity. The proposed indication for benralizumab is for add-on maintenance treatment for severe asthma with an eosinophilic phenotype in adult patients 18 years of age and older. The proposed dosing for benralizumab is 30 mg of solution in a single–dose, accessorized pre-filled syringe to be administered by a healthcare provider (per the labeling) subcutaneously every 4 weeks for 3 doses then every 8 weeks thereafter. The Sponsor anticipates long-term use of the medication consistent with the chronic nature of asthma.[b]

Though benralizumab is not approved or marketed in any country, there are two FDA approved monoclonal antibodies (Reslizumab and Mepolizumab) used for the treatment of severe asthma with an eosinophilic phenotype that work through the interleukin 5 (IL-5) pathway.[1,2] Neither of these biologics are approved with a REMS, but Reslizumab, an IL-5 antagonist, has a boxed warning for anaphylaxis.[2] Mepolizumab, also an IL-5 antagonist, carries a warning and precaution for hypersensitivity reactions, including anaphylaxis.[1]

[a] Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761070 relevant to this review:

- 11/16/2016: BLA 761070 submission for add-on maintenance treatment for severe asthma with an eosinophilic phenotype received
- 05/11/2017: A Post Mid-cycle communication meeting was held with the Agency and the sponsor by teleconference. The Agency informed the sponsor that based on the currently available data, a REMS was not anticipated, but the final decision on the need for a REMS would require a full review.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Asthma affects 7.4% of the adult US population over 18 years of age. In the US asthma is associated with a mortality rate of 14.1 persons per million and 1.8 million emergency department visits yearly.[3c] Asthma sufferers experience wheezing, breathlessness, coughing, and chest tightness. Pathophysiologically asthma is characterized by airway inflammation, with initially reversible airflow obstruction, and bronchial hyper responsiveness. Inflammation in the airways includes eosinophils, mast cells and other inflammatory markers. Asthma with eosinophilia is the most common inflammatory phenotype in severe asthma sufferers.[4] Severe asthma impacts 5-15% of asthma sufferers[4,5d] and has been defined as "asthma that requires treatment with high dose inhaled corticosteroids plus a second controller and/or systemic corticosteroid(s) to prevent it from becoming ''uncontrolled'' or that remains ''uncontrolled'' despite this therapy." [6] Patients with uncontrolled asthma experience symptoms throughout the day, awaken at night with symptoms, are unable to participate in normal activities and miss school and work. [7] Patients with severe asthma are at risk for asthma exacerbations resulting in emergency department visits, hospitalizations, death and the need for more aggressive treatment with increasing risk.[4, 8]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

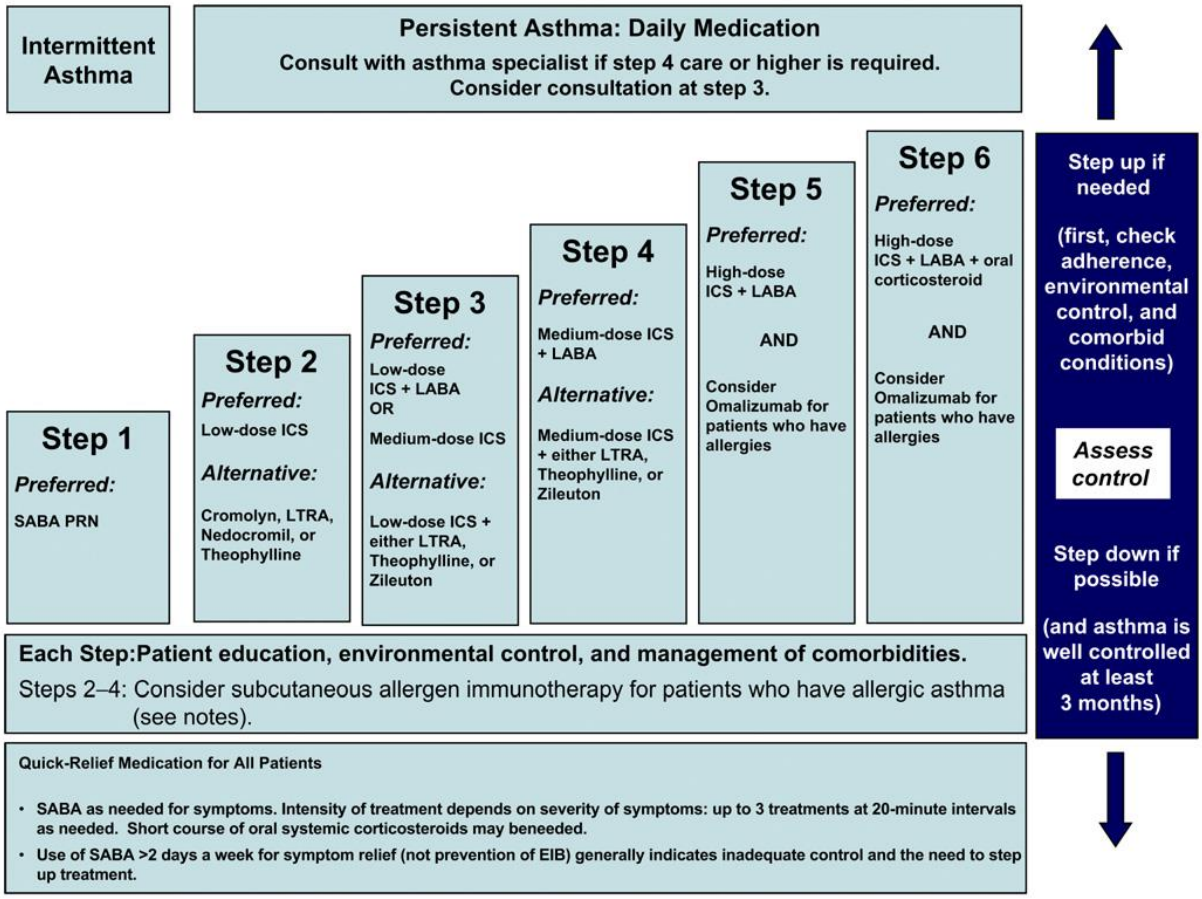
National and international guidelines for asthma uses a stepwise approach for treatment based on control and severity.[9] Patients with severe asthma receive steps 5 and 6 therapy (figure 1) and are exposed to high dose inhaled corticosteroids (ICS), and at step 6 oral corticosteroids (OCS). Significant risks associated with high dose inhaled corticosteroids include candida albicans infections of the upper airway, immunosuppression, adrenal suppression, reduction in bone mineral density, glaucoma, and cataracts.[10] Patients requiring chronic oral corticosteroids are at enhanced risk for the former side effects as well as additional serious multisystemic problems. [11]

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] FDAA factor (A): The estimated size of the population likely to use the drug involved.

In addition to receiving ICS, patients with severe and poorly controlled asthma should receive a long-acting beta2-adrenergic agonist (LABA).[9] LABA's have a class boxed warning for increased risk of asthma-related death. LABA's can lead to paradoxical bronchospasm, and may cause hypokalemia, and hyperglycemia. LABA's beta adrenergic stimulation limit their use in patients with cardiovascular or central nervous system disorders, diabetes mellitus, convulsions, and thyrotoxicosis.[12] Omalizumab is an anti-IgE monoclonal antibody that can be useful for patients with allergic asthma and is in national guidelines for stepwise therapy for patients with severe asthma. Omalizumab has a boxed warning for anaphylaxis.[13] Two other monoclonal antibodies, reslizumab and mepolizumab, both work via the IL-5 pathway, like benralizumab, but have different mechanisms of action. Reslizumab and mepolizumab are approved by the FDA for severe asthma with an eosinophilic phenotype but are not currently incorporated into national guidelines.[1,2,14] Reslizumab has a boxed warning for anaphylaxis.[2]

Figure 1



ICS= Inhaled corticosteroids LABA= Long Acting β_2 agonist SABA = Short Acting β_2 agonist

FIG 16. Stepwise approach for managing asthma in youths _12 years of age and adults.* PRN, As necessary.[9]

4 Benefit Assessment

The safety and efficacy of benralizumab in the treatment of severe eosinophilic asthma has been evaluated in a clinical development program. This included two pivotal multicenter, international, randomized, double-blind, placebo-controlled, parallel group exacerbation and safety clinical trials of 48 or 56 weeks duration (SIRROCO 17, and CALIMA 18) and an oral corticosteroid (OCS)-reduction and safety study (ZONDA 21) which lasted for 28 weeks. One additional phase 3 study (BISE) evaluated patients with mild to moderate asthma and one open label study (GREGALE) (b) (4) There are two additional ongoing studies to examine the long-term safety of benralizumab (Studies BORA 21 and MELTEMI 37). BORA 21 had blinded safety data submitted with the application, MELTEMI 37 has not had any data submitted at this time.

The pivotal studies evaluated the occurrence of exacerbations in patients receiving both ICS and LABA as baseline therapies and still uncontrolled with a history of at least two asthma exacerbations in the previous year. Adults and adolescents 18-75 were included in these studies. Initially planned for patients on high dose ICS, patients on medium dose ICS were included in study 18 to provide a descriptive analysis of the response of these patients. Patients were randomized to treatment for 48 weeks (SIRROCO 17) or 56 weeks (CALIMA 18):
Treatment groups consisted of patients randomized to receive subcutaneous administration of:

1. Benralizumab 30 mg given every 4 weeks throughout the study- study group (Q4W).
2. Benralizumab 30 mg given every 4 weeks for the first 3 weeks then every 8 weeks thereafter, with placebo given on weeks when benralizumab was not administered- study group (Q8W)
3. Placebo given every 4 weeks-study group (placebo).

Randomized patients were stratified by baseline blood eosinophil counts ≥ 300 cell/uL or ≤300 cell/uL at a 2:1 ratio. The primary endpoints for these studies were asthma exacerbations rate (AER) in patients with an eosinophilic count >300. An exacerbation was defined as:

- Use of systemic corticosteroids or a temporary increase in a stable oral corticosteroid background dose for at least 3 days
- An emergency room visit due to asthma that required systemic corticosteroids
- An inpatient hospitalization due to asthma

Patients with eosinophil count ≥ 300 comprised the population for the primary efficacy analysis. Secondary analyses included changes in Forced expiratory volume at 1 second (FEV_1) and Asthma Control Questionaire-6 (ACQ-6), an asthma patient reported outcome questionnaire. Both studies (17 & 18) were powered to detect a 40% reduction in exacerbations in both benralizumab dosing regimens compared to placebo.

In pivotal study SIROCCO (17), 1204 patients were randomized and received treatment; 399 patients to benralizumab Q4W, 398 patients to benralizumab Q8W, and 407 patients to placebo. Both baseline eosinophil count and a greater number of exacerbations in the previous 12 months were predictive of efficacy.

In pivotal study CALIMA (18), 1306 patients were randomized; 425 patients to benralizumab Q4W, 441 patients benralizumab Q8W, and 440 patients to placebo. Both baseline eosinophil count and greater number of exacerbations in the previous 12 months were predictive of efficacy.

Annual exacerbation rate associated with adjudication ER visit and/or hospitalization for SIROCCO and CALIMA in eosinophil high population* integrated data: Full Analysis Set data.[15]

Benralizumab at both Q4wk and Q8wk dosing demonstrated that the rate of ER visits or hospitilization for patients receiving benralizumab was less than that of placebo treated patients. A rate ratio less than one favors treatment with benralizumab compared to placebo.

	Q4 N = 516	Q8 N = 506
Exacerbation requiring adjudicated ER visit or hospitalization		
Rate ratio (benra/placebo)	**0.71**	**0.62**
95% confidence interval	0.47, 1.07	0.41, 0.95
p-value	0.106	0.029
Adjudicated hospitalization		
Rate ratio (benra/placebo)	**0.73**	**0.80**
95% confidence interval	0.42, 1.28	0.46, 1.39
p-value	0.270	0.432
*peripheral blood eosinophil count ≥ 300 cells/mcl and high-dose ICS population		

In the two pivotal studies CALIMA (18) & SIROCCO (20), 46 adolescents age ≥12 and < 18 had eosinophil counts >300 and were eligible for analysis. There was no evidence of a beneficial effect in any outcome for this age group.

ZONDA Study (20) was a multicenter, global, randomized double blind placebo control trial of adult patients. ZONDA studied the same dosing regimens used in the pivotal studies and 72 patients received Q4W benralizumab, 73 patients received Q8W benralizumab and 75 patients received placebo. All patients were on OCS and all had an eosinophil count ≥300. Two hundred and twenty patients were randomized; all patients received treatment. Zonda was a shorter study lasting for 28 weeks. The primary endpoint was the reduction in oral corticosteroid use expressed as a percentage change.

Summary of Efficacy: ZONDA[15]

	30 mg Q4 N = 72	30 mg Q8 N = 73	Placebo N = 75
% reduction in OCS dose from baseline			
Mean	56	58	20
Estimate for difference	33	38	
95% CI	17, 50	21, 50	--
p-value	<0.001	<0.001	--

After a review of the clinical trial program, the Medical Officer concluded "the sponsor has completed two pivotal efficacy and safety trials which demonstrate a statistically significant and clinically relevant improvement in asthma exacerbations in patients with severe asthma on maximum background standard of care. In addition, a third trial demonstrates a decrease in the use of oral corticosteroids required to control a patient's underlying asthma."[15]

5 Risk Assessment & Safe-Use Conditions

The population providing the safety information for benralizumab consists of:

11 completed clinical studies involving 3882 patients with asthma.

- Phase 2 & 3; 3811 patients received benralizumab
  - 2514 exposed to greater than 1 dose of benralizumab

The safety analysis based on the pivotal studies SIROCCO and CALIMA included 2510 patients who received study drug. Eight hundred forty one patients received benralizumab 30mg Q4W, 822 patients received benralizumab 30mg Q8W, and 847 received placebo. Exposure to the treatment lasted for 48-52 weeks with 1387 patients receiving benralizumab 48 weeks or more. The overall incidence of treatment emergent adverse events (TEAEs) during the on study period was similar among the three groups: 73.8% in the benralizumab Q4W, 73.6% in the benralizumab Q8W group, and 78.0% in the placebo group. Discontinuations due to TEAEs were higher in the benralizumab Q4W (2.0%) and Q8W (2.2%), than the placebo group (0.8%). Uriticaria was the leading common cause of discontinuation in the treatment group.[16]

Study 20, a phase 3 oral corticosteroid sparing study provided additional core safety data and included 220 patients; 72 on benralizumab Q4W, 73 on benralizumab Q8W and 75 on placebo. For this study, TEAEs in the on study period were lower in the benralizumab groups' 68.1% Q4W and 75.3% Q8W than the 82.7% in the placebo group. The pyrexia seen in studies 17 & 18 was not present in study 20; this is potentially related to their oral corticosteroid use.

5.1 DEATHS

In studies, 17 & 18 CALIMA/SIROCCO & 20 Zonda, 14 patients died during the on treatment and post treatment period. See table 2 below for cause of death and treatment group.

Table 2. Cause of Death by individual patient in pivotal studies 17 & 18 & 20.

	30mg Q4W Benralizumab	30mg Q8W Benralizumab	Placebo
Cause of Death *	Cerebral Hemorrhage	Cardiac Failure	Pulmonary Embolism
	Asthma	Overdose	Death (unknown cause)
	Completed suicide	Death (unknown cause)	Myocardial Infarction (post treatment)
	Road Traffic Accident	Sudden Death (post treatment)	Colon Neoplasm
	Acute Myocardial Infarction	Pneumonia	

*Each cell describes the cause of death in a single patient.

In a nonpivotal placebo controlled trial a 65 year old with multiple comorbid conditions post pancreatic resection/CV history, asbestos exposure, current amiodarone treatment developed severe pancytopenia 27 days after receiving his last dose of benralizumab.

The clinical medical officer stated that none of the deaths in the clinical trials could be attributed to benralizumab.

5.2 SERIOUS ADVERSE EVENTS

During the on-treatment period in pivotal studies 17 and 18, 11.9% (299 patients) had SAEs; 10.9% on Q4W benralizumab, 11.2% on Q8W benralizumab and 13.6% on placebo (as percentages of the 11.9% total). Asthma exacerbations and pneumonia were the most common SAEs. Asthma exacerbations occurred with greater frequency in the placebo group. There was no evidence that benralizumab treatment increased the occurrence of pneumonia.

5.3 ADVERSE EVENTS OF SPECIAL INTEREST

5.3.1 Risk of hypersensitivity, allergic reactions/immune reactivity:

Allergic reactions and hypersensitivity reactions are a risk with any foreign protein and occur with other monoclonal antibodies.[14,17] Hypersensitivity reactions had a similar incidence across groups during the on treatment period: 3.1% in the Q4W group, 2.9% in the Q8W group and 3.3% in the placebo group.

There were two cases of anaphylaxis that the sponsor attributed to a peanut allergy in a single patient on Q8W benralizumab, with known allergy to peanuts, who continued to receive benralizumab without issue. One patient in the Zonda study withdrew 7 days after stopping treatment and on the same day as an "allergic reaction", the reaction was considered severe and related to thebenralizumab 30mg Q4W. During the non-pivotal trials, a patient experienced an anaphylactic reaction 1 hour and 45 minutes after the fourth dose of 100 mg of benralizumab, which was assessed as related to the IP by the investigator and resulted in discontinuation of the IP. In the 120 day safety update there was a case of anaphylaxis associated with the IP that led to epinephrine administration and drug withdrawal. Hypersensitivity reactions are to be identified in the warnings and precautions section in labeling.

Monoclonal antibodies can lead to anti-drug antibodies and result in immune complex diseases or hypersensitivity type III reactions. No cases of immune complex disease were reported in studies 17, 18 or 20. Antidrug antibodies developed in benralizumab treated patients, but these did not appear to be related to changes in efficacy or safety, as reported by the sponsor and confirmed by the clinical medical officer's assessment.

5.3.2 Risk of Serious Infections:

Benralizumab's mechanism of action leads to a potential risk of serious infections. Serious infections and infestations occurred during the on treatment period in 1.4% Q4W benralizumab, 2.2% Q8W benralizumab and 2.2% placebo group. Incidence and infection type did not differ between the groups. Serious Herpes Zoster infection occurred in one patient in Calima and one in a non pivotal study. These patients were on confounding concomitant medications, methotrexate and systemic steroids, at the time of the herpes infection. Further analysis of herpes zoster infections suggested by the FDA[e] were similar across groups with 0.4% patients in the Q4W, and 0.7% in the Q8W benralizumab and 0.7% in the placebo group experiencing a herpes zoster infection. The concern for herpes zoster infection is heightened by an increased risk of serious herpes zoster infection seen in Mepolizumab, which also works through the IL-5 pathway. No additional labeling for this risk is planned at this time, but routine pharmacovigilance is recommended.

6 Expected Postmarket Use

Benralizumab will likely be distributed by specialty pharmacies, closed systems or office based prescribers.. The proposed labeling states that Benralizumab is to be administered by a health care provider.

The indication for benralizumab is for use in patients with severe asthma. National guidelines identify that patients with severe asthma should be treated by specialists in asthma care. These specialists, who

[e] Correspondence Meeting Minutes Type B Pre-BLA September 20, 2016 IND 100237

should be familiar with the management of severe asthma, should understand the risks of treatment including hypersensitivity reactions and are able to respond to medical emergencies associated with this class of medicines specifically the occurrences of hypersensitivity reactions in the outpatient setting. [9,18,19]

7 Risk Management Activities Proposed by the Sponsor

The Sponsor did not propose any risk management activities for benralizumab beyond routine pharmacovigilance and labeling. The Sponsor acknowledges routine pharmacovigilance will be undertaken to evaluate the aftermarket safety of benralizumab with particular attention paid to the risk of serious infections and helminth infection. [f] [20]

8 Discussion of Need for a REMS

The Clinical Medical Officer Reviewer recommends approval of benralizumab on the basis of the efficacy and safety information currently available.

Severe eosinophilic asthma is a chronic respiratory disorder with hyperreactive airways and inflammatory changes that leave patients with difficulty breathing, cough and impairment in daily function, including work and leisure activities and an increased risk of death. Both long-term beta agonists and steroids the treatment options for most patients with severe asthma carry significant risks and provide inadequate benefit to patients with severe asthma. Three randomized double blind placebo controlled trials demonstrated the effectiveness of benralizumab for the treatment of severe asthma with an eosinophilic predominance in patients on long acting beta agonists with or without oral corticosteroids. [20] The risks of benralizumab are similar to other biologics used in the population of patients with severe asthma. These risks are allergic and immunologic, including the risk of severe infections, and although not seen in the clinical trials, helminth infections will be addressed in the labeling. Additionally, warnings that benralizumab is not to be used in acute asthma exacerbations and to not stop oral corticosteroids abruptly will be stated in the labeling, Benralizumab is likely to be prescribed and administered by health care providers able to recognize and respond to both acute reactions as well as monitor for and recognized the risk of serious infection. National guidelines recommend severe asthma should be treated by specialists with an expertise in the treatment of severe asthma. These risks can be addressed with warnings and precautions adequately communicated through labeling and are familiar to the anticipated prescribing populations for benralizumab. Therefore, further mitigation beyond labeling is not required.

[f] AstraZeneca Clinical Overview Clinical Risks October 30, 2016 p78

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, it is the opinion of this reviewer that a REMS is not necessary for benralizumab to ensure the benefits outweigh the risks. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

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/s/

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