CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

Date:	August 7, 2015
Reviewer(s):	Jasminder Kumar, Pharm.D. Division of Risk Management (DRISK)
Acting Team Leader:	Jamie Wilkins Parker, Pharm.D., DRISK
Acting Deputy Division Director:	Reema Mehta, Pharm.D., M.P.H., DRISK
Subject:	Review evaluates if a REMS is needed for Nucala (b) (4)
Drug Name:	Nucala (b) (4) (mepolizumab) lyophilized powder for injection
Therapeutic Class:	Humanized monoclonal antibody (IgG1 kappa) targeting human interleukin 5 (IL-5)
Dosage form and route:	Lyophilized powder for subcutaneous injection (100 mg of mepolizumab per single-use vial)
Application Type/Number:	BLA 125526
Applicant/sponsor:	GlaxoSmithKline LLC
OSE RCM #:	2014-2451

CONTENTS

1 INTRODUCTION

The purpose of this review is to provide the Division of Risk Management's (DRISK) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME), Nucala (mepolizumab). On November 4, 2014, the Agency received BLA 125526 from GlaxoSmithKline, LLC for mepolizumab. The proposed indication is for the treatment of severe eosinophilic asthma, identified by blood eosinophils greater than or equal to 150 cells/µL at initiation of treatment or blood eosinophils greater than or equal to 300 cells/µL in the past 12 months, as add-on maintenance treatment in patients aged 12 years and older. The Applicant did not submit a proposed REMS but did submit a proposed risk management plan for mepolizumab, which included routine pharmacovigilance, a pregnancy registry, and recommendations for labeling.

1.1 PRODUCT BACKGROUND

Mepolizumab is a humanized monoclonal antibody (IgG1 kappa) that targets human interleukin 5 (IL-5) with high affinity and specificity. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils (multiple cell types, including eosinophils, are involved in inflammation). Mepolizumab binds to IL-5, inhibiting the bioactivity of IL-5 (b) (4) by blocking the binding of IL-5 to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface, thereby inhibiting IL-5 signaling and reducing the production and survival of eosinophils. The proposed indication for mepolizumab is for the treatment of severe eosinophilic asthma, identified by blood eosinophils greater than or equal to 150 cells/µL at initiation of treatment or blood eosinophils greater than or equal to 300 cells/µL in the past 12 months, as add-on maintenance treatment in patients aged 12 years and older. It should not be used to treat acute asthma symptoms or acute exacerbations.

The proposed dosing for mepolizumab is 100mg administered subcutaneously once every 4 weeks. Mepolizumab is a lyophilized powder for injection available in single use vials that must be reconstituted and administered by a healthcare professional. Monitoring of patients after administration should be considered. Patients should not discontinue systemic or inhaled corticosteroid (ICS) abruptly upon initiation of therapy with mepolizumab and those with pre-existing helminth infections should be treated prior to starting therapy with mepolizumab.

1.2 DISEASE BACKGROUND

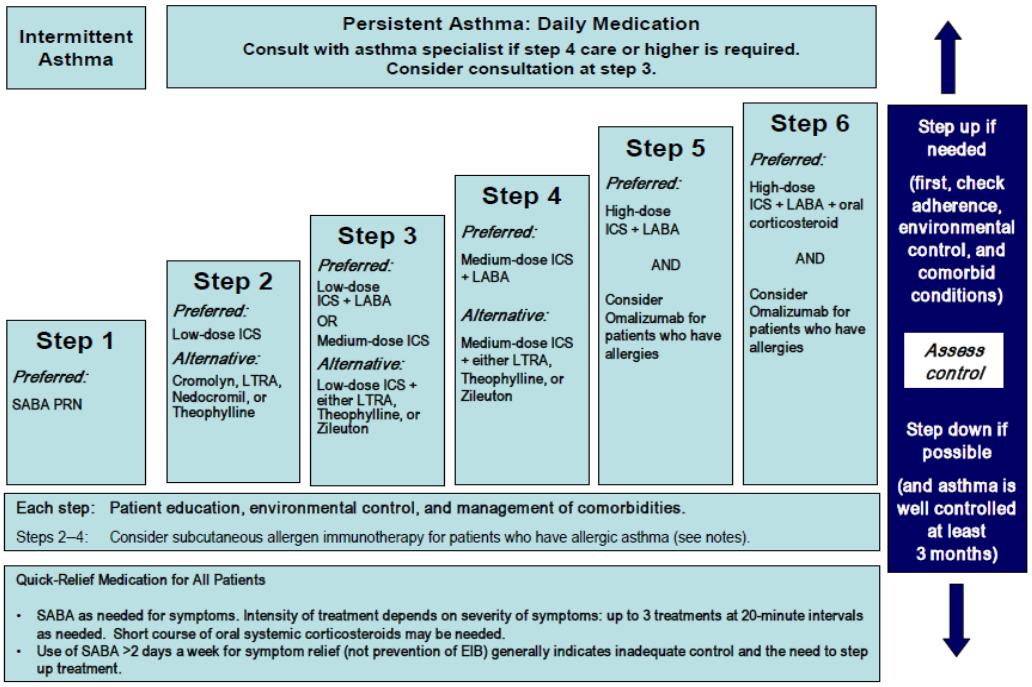
Asthma is a chronic inflammatory disease of the airways that affects approximately 25.7 million people in the United States, including 7 million children under the age of 18.[1] Airway inflammation contributes to airway hyperresponsiveness, airflow limitation, respiratory symptoms, and disease chronicity. The National Institutes of Health, National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 (EPR3), describe asthma as a disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T-lymphocytes, macrophages, neutrophils, and epithelial cells. This inflammation can also cause recurrent episodes of wheezing, breathlessness, chest tightness, and

[1] Centers for Disease Control and Prevention: National Center for Health Statistics, National Health Interview Survey Raw Data, 2009. Analysis by the American Lung Association Research and Program Services Division using SPSS and SUDAAN software.

coughing, especially at night or in the early morning. Episodes may be associated with variable airflow obstruction that is reversible either spontaneously or with treatment. However, airway obstruction in asthma may become irreversible.[2] Asthma prevalence has increased from 3.1% in 1980 to 5.5% in 1996 and 7.3% in 2001 to 8.4% in 2010 and is more likely to occur in Blacks when compared to both Whites and Hispanics, females, and in those with a lower annual household income.[3] Asthma related costs include both direct health care costs, as well as indirect costs (e.g. lost productivity).

The severity of asthma is classified by using domains of current impairment and future risk, which includes symptoms, use of a short-acting-beta$_2$-agonist (SABA) for quick relief, exacerbations, and pulmonary functions. Severe asthma affects less than 10% of patients with asthma.[4] The goals of asthma treatment include improving quality of life for people who have asthma in addition to controlling symptoms, reducing the risk of exacerbations, and preventing asthma-related death. The majority of patients with asthma can be adequately controlled by following a step-wise treatment approach, as described in the figure below.[2]

Figure 1: Stepwise Approach for Managing Asthma in Youths ≥12 Years of Age and Adults



— Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** EIB, exercise-induced bronchospasm; ICS, inhaled corticosteroid; LABA, long-acting inhaled beta$_2$-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

[2] National Institutes of Health, National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Full Report of the Expert Panel: Guidelines for the Diagnosis and Management of Asthma (EPR-3). July 2007, http://www nhlbi nih.gov/guidelines/asthma.

[3] CDC National Center for Health Statistics, National Health Interview Survey (NHIS) National Surveillance of Asthma: United States, 2001-2010.

[4] Custovic A, Johnston SL, Pavord I, et al. EAACI position statement on asthma exacerbations and severe asthma. Allergy. 2013;68:1520-31.

However, a minority of patients experience uncontrolled asthma despite attempts to control their disease using the step-wise treatment recommendations.[5] Newer therapies have focused on interrupting the inflammatory processes that play a central role in the pathophysiology of asthma. Xolair (omalizumab) is a recombinant humanized monoclonal antibody (IgG1) that inhibits the binding of IgE to the high-affinity IgE receptor (FcεR1) on the surface of mast cells and basophils, resulting in receptor down regulation and inhibition of inflammatory mediator release.

One subset of asthma patients that is most likely to benefit from specific anti-inflammatory therapies is characterized by increased numbers of eosinophils in their airways. Interleukin-5 (IL-5) plays a large role in promoting eosinophil growth and activation in the tissues. IL-5 targets may contribute to reducing eosinophil maturation, migration, and survival.[6] There are no currently FDA-approved products that target IL-5, at this time.

1.3 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 125526 relevant to this review:

November 4, 2014: The Agency received a BLA submission for mepolizumab. The submission did not include a proposed REMS but did submit a proposed risk management plan for mepolizumab, which includes routine pharmacovigilance, a pregnancy registry, and targeted follow-up questionnaires to monitor cardiovascular safety.

April 28, 2015: A Mid-Cycle meeting was held between the Agency and the Sponsor via teleconference. The Agency informed the Sponsor that based on the currently available data, a REMS was not needed for mepolizumab.

June 11, 2015: A Pulmonary-Allergy Drugs Advisory Committee Meeting was held to discuss the safety and efficacy of mepolizumab. The committee voted 14-0 in favor that the efficacy and safety data support approval of mepolizumab 100 mg SC once every 4 weeks for the treatment of severe asthma in adults, 18 years of age and older and voted 4-10 against approval for use in adolescents 12-17 years of age with severe asthma.

2 MATERIALS REVIEWED

The following is a list of materials that informed our review:

- GlaxoSmithKline LLC. Risk Management Plan for Nucala (mepolizumab), dated November 4, 2014.
- GlaxoSmithKline LLC. Clinical Overview Nucala (mepolizumab), dated November 4, 2014.
- GlaxoSmithKline LLC. Summary of Clinical Safety Nucala (mepolizumab), dated November 4, 2014.
- GlaxoSmithKline LLC. Summary of Clinical Efficacy Nucala (mepolizumab), dated November 4, 2014.

[5] Centers for Disease Control and Prevention. Vital signs: asthma prevalence, disease characteristics, and self-management education: United States, 2001–2009. MMWR Morb Mortal Wkly Rep. 2011;60(17): 547–552.

[6] Walford HH, Doherty TA. Diagnosis and management of eosinophilic asthma: a US perspective. *Asthma Allergy*. 2014. Apr 11;7:53-65

- GlaxoSmithKline LLC. Proposed Prescribing Information for Nucala (mepolizumab), dated November 4, 2014, updated July 21, 2015.
- Chaudhry S. Division of Pulmonary, Allergy, and Rheumatology Products, Clinical Review for BLA 125526, dated June 30, 2015.

3 REVIEW FINDINGS FOR MEPOLIZUMAB

3.1 OVERVIEW OF CLINICAL PROGRAM AND EFFICACY

The safety and efficacy of mepolizumab in the treatment of severe eosinophilic asthma has been evaluated in a severe asthma clinical development program that consisted of three multicenter, randomized, double-blind, placebo-controlled, parallel group clinical trials of 24-52 weeks' duration in 1,327 subjects aged 12 years and older. The program consisted of two exacerbation and safety studies (Study 97 and Study 88) and an oral corticosteroid (OCS)-reduction and safety study (Study 75). The trials were designed to evaluate the efficacy of mepolizumab administered once every 4 weeks in subjects not controlled on their current asthma drug therapy. There are also two additional ongoing open-label extension (OLE) studies to examine the long-term safety of mepolizumab (Study 66 and Study 61).

Study 97 and Study 88, evaluated the frequency of clinically significant exacerbations of asthma, defined as worsening of asthma requiring use of oral/systemic corticosteroids and/or hospitalization and/or emergency department visits. During the trials, subjects continued their baseline asthma therapy. The primary endpoint was frequency of clinically significant exacerbations of asthma as defined by: worsening of asthma which in the investigator's opinion required use of oral/systemic corticosteroids and/or hospitalization and/or emergency department (ED) visits. Some key secondary endpoints included: rate of clinically significant exacerbations requiring hospitalizations or ED visits, rate of clinically significant exacerbations requiring hospitalization, change from baseline in clinic pre-bronchodilator forced expiratory volume in 1 second (FEV_1), and changes from baseline in St. George's Respiratory Questionnaire Score (SGRQ).

Study 97 was a 52-week dose-ranging and exacerbation study in which patients were randomized 1:1:1:1 to receive either mepolizumab 75mg IV, 250mg IV, 750mg IV, or placebo. The primary endpoint was met and was statistically significant in all mepolizumab groups compared with the placebo group. Reductions in exacerbation rate compared to placebo with mepolizumab 75mg was 48% reduction (95% CI; 0.39, 0.69), mepolizumab 250mg was 39% reduction (95% CI; 0.46, 0.81), and mepolizumab 750mg was 52% reduction (95% CI; 0.36, 0.64). A decrease of 60% compared with placebo was observed with 75 mg IV (p=0.11) for exacerbations requiring ED visits or hospitalizations.

Study 88 was a 32-week exacerbation double-dummy study in which patients were randomized 1:1:1 to receive either mepolizumab 75mg IV + placebo SC, mepolizumab 100mg SC + placebo IV, or placebo SC + placebo IV. Based on results from Study 97, the 100-mg SC dose was chosen since it provides comparable systemic exposure to that of mepolizumab 75 mg IV. In subjects treated with mepolizumab 100mg SC, the percent reduction in the frequency of clinically significant exacerbations (53%), as well as the percent reduction in the frequency of

exacerbations that required hospitalization (69%, p=0.034) or emergency department visits (61%, p=0.015), compared with placebo, were statistically significant.

Study 75 was a 24-week steroid reduction study that evaluated the ability to reduce maintenance OCS while maintaining asthma control in OCS-dependent patients. There was OCS an optimization phase prior to randomization to ensure that the dose of OCS was at the lowest effective dose to maintain asthma control. Further OSC reduction was initiated 4 weeks after randomization. Asthma control was defined as subjects experiencing no exacerbations during the maintenance treatment phase of the trial (Weeks 20-24). The primary endpoint was the number of subjects at Weeks 20-24 in the following categories: percent reduction of OCS dose compared with the baseline dose (90% to 100% reduction, 75% to <90%, 50% to <75%, >0% to <50%), no decrease in OCS, lack of control during Weeks 20-24, or withdrawal from treatment. Subjects receiving mepolizumab were able to achieve greater reductions in daily OCS dose, while maintaining asthma control, compared with subjects treated with placebo (p=0.008). During Weeks 20-24, more than half of subjects treated with mepolizumab (54%) achieved a >50% reduction from baseline in daily OCS dose compared with 33% of subjects treated with placebo (p=0.027). The median percentage reduction from baseline in the daily OCS dose was 50% in the mepolizumab group compared with 0% in the placebo group (p=0.007).

Regarding secondary endpoints, statistically significant improvements in FEV_1 and peak expiratory flow (PEF) were seen in Study 88 and 75, but not Study 97, for both measures. In regards to asthma control, all three studies showed improvement using the Asthma Control Questionnaire (ACQ), but ACQ was not statistically significant at Week 52 for Study 97. Health-related quality of life was measured using SGRQ in Study 88 and 75 (but not measured in Study 97), with a statistically significant improvement in both trials. Finally, treatment with mepolizumab 100mg SC or 75mg IV resulted in reduction of blood eosinophils, which was sustained over duration of treatment in the exacerbation studies.

The 100mg SC dose and route proposed for marketing are supported by the lack of differential dose-response seen in Study 97, similar treatment effects of the 75mg IV and 100mg SC dose in Study 88, and supporting PK/PD IV to SC bridging data from Study 92.

Study 61 (MEA115661) and Study 66 (MEA115666) are ongoing OLE studies for subjects who completed Study 88/Study 75 and Study 97, respectively. These studies were designed to evaluate the long-term safety and efficacy for mepolizumab. Patients in Study 61 had at least a 12-month treatment break between the end of the double-blind study and the start of the open-label study. All patients in the double-blind studies were switched to mepolizumab 100mg SC every 4 weeks for a total of 52 weeks and up to 3.5 years for OLE Study 61 and Study 66, respectively. The primary endpoints for both OLE studies are the frequency of AEs, including both systemic and local site reactions. Secondary endpoints include: frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies, annualized rate of exacerbations, Asthma Control Questionnaire (ACQ-5) score, FEV_1, number of withdrawals due to lack of efficacy, number of withdrawals due to AEs, number of hospitalizations due to AEs including asthma exacerbations, frequency of both systemic and local site reactions, 12-lead ECG parameters, vital signs, and clinical laboratory parameters. In the OLE studies, improvements in asthma control, including exacerbation rate, FEV_1, and ACQ-5, were maintained thus far.

3.2 SAFETY CONCERNS

For the purposes of this review, an adverse event (AE) was defined as any untoward medical occurrence in a subject temporally associated with the use of mepolizumab, whether or not considered related to mepolizumab. Therefore, in the mepolizumab clinical development program, an AE included exacerbations of a chronic or intermittent pre-existing condition.

Common Adverse events (AE)

The overall safety population included a total of 1,327 patients with severe eosinophilic asthma, in the clinical development program consisting of three randomized, placebo-controlled, multicenter Phase 3 clinical trials. Of these patients, there were 915 who received at least one dose of mepolizumab.

The overall incidence of AEs was similar between placebo (82%) and the mepolizumab (79% 100mg SC and 83% 75mg IV) doses equal to the 100 mg SC formulation to be marketed. The most frequently reported AEs seen with mepolizumab were headache (18% of subjects in the placebo group, 20% in mepolizumab 100mg SC, and 23% in mepolizumab 75mg IV) and nasopharyngitis (19% of subjects in the placebo group, 16% in mepolizumab 100mg SC, and 23% in mepolizumab 75mg IV. In general, the AE profile was similar between routes of administration (IV or SC) with the exception of a higher rate of injection site reactions with SC administration (8% with SC administration vs 3% with IV administration), as expected. A total of 67 (16%) subjects in the placebo group and 183 (20%) subjects in the mepolizumab group experienced any drug-related AE.

Of the 35 patients that discontinued, the incidence of AEs being the cause of discontinuation was higher in the placebo group (3%) than the mepolizumab 100mg SC and 75mg IV groups (1% each). The most common reason for discontinuation was withdrawal of consent (4%). The most frequent AE that lead to discontinuation was asthma (3 subjects in the placebo group, 1 in the mepolizumab 75mg IV group, and 0 in the mepolizumab 100mg SC group).

3.2.1 Serious Adverse Events (SAEs)

A total of 155 subjects in the severe asthma studies reported SAEs, with 15% in the placebo group, 6% in the mepolizumab 100mg SC group, and 10% in the mepolizumab 75mg IV group. The cause of the difference in SAE's between groups was due to a larger incidence of asthma exacerbation in subjects receiving placebo. The incidence of SAEs in the OLE was similar to the placebo-controlled severe asthma studies, with 8% and 9% in Study 61 and Study 66, respectively.

A total of 8 deaths were reported in the severe asthma program, 5 in the placebo controlled severe asthma (PCSA) studies, and 3 in the OLE study. In the PCSA studies, there were two deaths in the placebo group and four deaths in the mepolizumab group. All deaths were considered unrelated to study drug by the investigator. The clinical reviewer concluded that the data does not suggest a treatment-related effect for these cases since the events are balanced across treatment arms. [7]

3.2.2 Adverse Events of Special Interest

For subjects with severe eosinophilic asthma in the mepolizumab program, AEs of special interest included cardiac events.

An imbalance in cardiac-related SAEs was seen from the clinical reviewer's evaluation of the safety data from Study 97.[7] In this study, there was an increase in cardiac, thromboembolic, and ischemic SAEs (3 in placebo group, 4 in mepolizumab 75mg IV, 2 in mepolizumab 250mg IV, and 4 in mepolizumab 750mg IV). However, this imbalance decreased when events were grouped into ischemic versus arrhythmogenic events. No imbalance was seen in Studies 88 and 75. Based on this potential signal, the Sponsor used an Independent Data Monitoring Committee and external adjudication panel to review cardiovascular safety that occurred during Phase 3 studies. A total of three events from Study 88 were adjudicated as cardiovascular (CV) or all-cause death. The committee concluded that there were too few overall CV events for a meaningful assessment and recommended continuation of the OLE studies. The clinical reviewer performed an analysis and found that there was a dose-dependent trend for CV events, particularly high dose 750mg IV. Although this imbalance was not seen with the dose proposed for marketing, the clinical reviewer notes that the data should be interpreted cautiously as the events occurred infrequently.[7]

3.3 SUMMARY OF SPONSOR'S PROPOSED RISK MANAGEMENT PLAN

The Sponsor has not proposed any risk mitigation beyond routine pharmacovigilance or labeling for the identified risks of local injection site reactions of systemic allergic and non-allergic reactions, the potential risks of infections, malignancies, immunogenicity, cardiovascular events, and exaggerated response of symptoms upon cessation of treatment, and missing data in patients with parasites or a high risk of parasitic infections . The Sponsor has proposed a pregnancy surveillance program (b) (4) for use in pregnancy.

4 DISCUSSION

Based on results of the Phase 3 trials, mepolizumab was found to be efficacious versus placebo for the treatment of severe eosinophilic asthma, identified by blood eosinophils greater than or equal to 150 cells/µL at initiation of treatment or blood eosinophils greater than or equal to 300 cells/µL in the past 12 months, as add-on maintenance treatment in patients aged 18 years and older. During the June 11, 2015, Pulmonary-Allergy Drugs Advisory Committee Meeting panelists voted against approval for use in adolescents 12-17 years of age. Due to the limited data in patients 12-17 years of age, the clinical reviewer recommends further evaluation of adolescents and younger pediatric patients to be completed as Pediatric Research Equity Act Post Marketing Requirement.[7]

The adverse event of special interest was cardiac events. The observed events in the clinical trials showed that cardiac events were not imbalanced. The clinical reviewer performed an analysis and found that there was a dose-dependent trend for CV events, particularly high dose 750mg IV. Although this imbalance was not seen with the dose proposed for marketing, the clinical reviewer notes that the data should be interpreted cautiously as the events occurred

[7] Chaudhry S. Division of Pulmonary, Allergy, and Rheumatology Products. Clinical Review, dated June 30, 2015.

infrequently. Due to the lack of sufficient evidence at this time, the label does not include any Warnings and Precautions regarding the risk at this time.

The clinical trials excluded use of mepolizumab in patients with parasitic infection. Therefore, the clinical reviewer has recommended a PMR in parasitic disease to evaluate this further.[7] In addition, the mepolizumab label includes information in the Warnings and Precautions, which cautions use in patients with pre-existing helminth infections and recommends temporary discontinuation of mepolizumab.

The most likely prescribers of mepolizumab are specialists who are familiar with the management of severe asthma, frequently monitor patients, and understand the risks of treatment. Mepolizumab is also indicated for administration by a healthcare professional. Therefore, with the lower incidence of serious and non-serious safety issues compared to placebo, as well as Warnings and Precautions adequately communicated through the labeling, DRISK does not recommend a REMS as necessary to ensure the benefits of mepolizumab outweigh the risks. Severe eosinophilic asthma is a chronic condition with few therapeutic options and overall, in subjects with severe eosinophilic asthma, the safety profile of mepolizumab plus standard of care was similar to placebo plus standard of care.

5 CONCLUSION AND RECOMMENDATIONS

In conclusion, risk mitigation measures beyond professional labeling are not warranted for mepolizumab. Based on the currently available data, the benefit-risk profile for mepolizumab is acceptable for the treatment of severe eosinophilic asthma, identified by blood eosinophils greater than or equal to 150 cells/µL at initiation of treatment or blood eosinophils greater than or equal to 300 cells/µL in the past 12 months, as add-on maintenance treatment in patients aged 18 years and older and a REMS is not warranted at this time.

Should the Division of Pulmonary, Allergy, and Rheumatology Products have any concerns or questions, or feel that a REMS may be warranted for this product, or if new safety information becomes available, please send a consult to DRISK.

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/s/

JASMINDER N KUMAR
08/07/2015

REEMA J MEHTA
08/07/2015
I concur.