Pharmacovigilance Plan Review

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To:	Jon Daugherty, PhD, Chair
Through:	Michael Nguyen, MD, Acting DE Director

Subject:	BLA 125473
Applicant:	Merck Sharp & Dohme Corp.
Product:	Standardized Allergenic Extract, Timothy Grass (Phleum pratense) MK-7243 GRASTEK Marketed as GRAZAX outside the US
Proposed Indication:	For treatment of diagnosed Timothy and related grass pollen induced allergic rhinitis, with or without conjunctivitis in adults and children 5 years of age and older
Submission Date:	25-JAN-2013
PVP Submission Date:	25-JAN-2013
Action Due Date:	17-APR-2014

1. Introduction

a. Product description

The product, referred to as GRASTEK, GRAZAX or MK-7243, is a fast-dissolving (e.g., less than 10 seconds), sublingual tablet for oromucosal delivery.

The active substance is a natural grass pollen extract which is partially purified and standardized from Timothy grass.

b. Pertinent regulatory history

i. Prior licensure

A Marketing Authorization Application for GRAZAX® (MK-7243) was filed by the Mutual Recognition Procedure in the European Union (EU) and was first approved in 2006 in Sweden. Subsequently, it has received marketing authorization in 30 countries.

GRAZAX is indicated in the EU for the disease-modifying treatment of grass pollen-induced rhinitis and conjunctivitis in adults and children (5 years or older) with clinically relevant symptoms and diagnosed with a positive skin prick test and/or specific IgE test to grass pollen.

c. Objectives/Scope of the review

The purpose of this memorandum is to summarize the sponsor's proposal for a post-market surveillance study to address a request by CBER for additional post-market monitoring for certain serious allergic reactions, and to document the sponsor's agreed upon commitments to conduct a post-market safety study. A full review of the pharmacovigilance plan and associated safety data was previously documented in the Pharmacovigilance review Memorandum, 11/13/2013.

2. Materials reviewed

a. Routine items:

i. Pharmacovigilance Plan:

STN 125473.0 **-** Section 1.11.4

ii. Pertinent sections of the licensing application selected by the reviewer

Post-market Commitment Concept Protocol, submitted by the sponsor on March 14, 2014, as an amendment to BLA 125473.

iii. Input from CBER Product, Clinical and Statistical reviewers

Final determination of the safety profile of the product used in the studies submitted to this BLA is pending final clinical, statistical and product reviews.

b. Other items (if available)

i. International postmarketing experience with the same product

GRAZAX has an estimated 112,981 patient-years of postmarketing use in Europe from initial licensure in 2006 through 30 SEP 2012.

A total of 1,268 spontaneous postmarketing healthcare provider reports were submitted to the sponsor through 30 SEP 2012, of which 116 were classified as serious. Of these 116 cases, 27 were assessed as serious systemic allergic reactions.
The most frequently reported spontaneous AEs were oral pruritus, edema mouth, lip swelling, throat irritation, and swollen tongue; the most frequently reported serious spontaneous AE was dyspnea.

Fatalities – spontaneous reports
No reported treatment-related fatalities were reported in the post-marketing safety data as of 30 SEP 2012.

Serious local allergic reactions– spontaneous reports
Thirty-five reports of serious local reactions have been received through SEP 2012; 11 of which overlap with the serious systemic allergic reaction reports.

EU-registration postmarketing support studies
A total of 1749 adult subjects with or without asthma participated in 6 post-EU approval market-support studies, 1666 who received MK-7243 at 2800 BAU dose daily. These studies were performed as life cycle management studies and not as post-approval commitment studies, e.g., related to specific safety issues.

The sponsor reports no new safety signals were identified, and the pattern of reported AEs was consistent with that observed in the clinical studies, with a predominance of local application site reactions. There was one serious anaphylactic reaction reported in these trials (Study GT-10), no reports of anaphylactic shock and one report of death (Study GT-15, extension phase).

Postmarketing studies and other post approval programs
To date, 20 MK-7243 observational postmarketing studies have been completed; four are ongoing; and one was cancelled. Approximately 8,500 subjects have been exposed to at least 1 dose of MK-7243 in these post-marketing trials with the majority of these subjects being adults. No deaths or treatment-related anaphylactic shock have been reported.

Periodic Safety Update Report
From 01-OCT-2012 through 30-APR-2013, a cumulative total of 139 spontaneous postmarketing reports of SAEs in MK-7243 recipients had been received by the sponsor.

Of these, ten reports of serious systemic allergic adverse events were reported, which were coded with one more of the following PT terms: anaphylactic reaction, anaphylactic shock and/or hypersensitivity.

Thirteen reports of serious asthmatic adverse events were reported based upon one or more of the following preferred terms: asthma, asthma exercise induced, bronchial hyperreactivity, bronchial obstruction, bronchospasm,

cough, dysphonia, dyspnoea, forced expiratory volume decreased, hyperventilation, obstructive airways disorder, peak expiratory flow rate decreased, prolonged expiration, asthma late onset, asthmatic crisis, reactive airways dysfunction syndrome, status asthmaticus and wheezing.

Six reports of serious local reactions with throat symptoms were reported based upon the following preferred terms: choking sensation, dysphagia, dysphonia, laryngeal edema, larynx irritation, oropharyngeal swelling, pharyngeal edema, stridor, throat tightness and upper airway obstruction. Four of the 6 reports were also classified a serious systemic allergic reaction, 2 of which were also classified as a serious asthmatic reaction. None of the 6 reports were reported as life-threatening or resulting in death.

3. Summary of Pharmacovigilance Plan Review (from PV Review Memo, 11/13/2013)

Specific anticipated or potential risks included systemic allergic reactions, including anaphylactic reactions and local allergic reactions with potential to compromise airway and acute worsening of asthma symptoms (exacerbation).

Based upon the product class and postmarketing experience outside the US, potential safety concerns that should be considered for enhanced surveillance include: Anaphylactic shock, Severe laryngopharyngeal disorders , Autoimmune disorders.

Selected limitations of the Clinical Safety Data for Grastek relative to the identified and potential risks include the following:

- Subjects with persistent and with moderate to severe asthma were excluded from the clinical studies and therefore, the safety of GRASTEK in this population has not been characterized. Also, individuals whose asthma is controlled with ICS or ICS/LABA combination therapy were not prospectively evaluated. Note: The sponsor states that sublingual immunotherapy in severe or uncontrolled asthmatics is a contraindication under current immunotherapy practice guidelines.

- Subjects with a history of anaphylaxis were excluded from the clinical studies.

- Subjects who had allergen immunotherapy within 5 years prior to enrollment were excluded from the clinical efficacy studies (a subset of the safety database).

- Subjects who were pregnant, not using adequate contraception or breast-feeding were excluded from participation in the studies.

The sponsor's proposed pharmacovigilance plan includes routine surveillance as well as specific measures to address the identified risks related to systemic allergic reactions, local reactions with potential for respiratory obstruction, and asthma exacerbation. These pharmacovigilance measures include follow-up questionnaires for reports of these reactions, specific labeling to address these risks, and ongoing phase 4 studies in Europe.

4. Integrated Risk Assessment

- **a.** The proposed pharmacovigilance measures are adequate for addressing the identified and potential risks and do not trigger a post-market requirement for a safety study.
- **b.** However, CBER requested that the sponsor augment their pharmacovigilance activities by proposing a study, to be conducted as a post-market commitment, to additionally monitor the risk of allergic reactions in the US should this product be licensed. While sublingual immunotherapy in severe or uncontrolled asthmatics is a contraindication under current immunotherapy practice guidelines, subjects with persistent and with moderate asthma were excluded from the clinical studies and therefore, the safety of GRASTEK in this population has not been characterized. Additionally, the potential for respiratory compromise in children due to their relatively smaller airway was noted, although such events have not been reported in the post-marketing setting to date. A postmarket study enrolling all patients prescribed the product without these exclusions could provide additional information on the incidence and risk factors for serious allergic reactions in the population using the product in actual use.
- **c.** OVRR contacted the sponsor with a request to submit a protocol synopsis for a postmarketing commitment (PMC) to conduct a Phase 4 safety study of GRASTEK in the population for whom the product would be approved in the US.
- **d.** The sponsor submitted the requested synopsis to Module 1.17.1 on March 14, 2014.

5. Review of Sponsor's Protocol Synopsis

- **a.** The sponsor proposed a post-market study, to be conducted in 2 large claims databases representing 50-60 milllion patients, that will identify all new users of Grastek based on dispensing claims. The sponsor initially proposed the study to run from initial marketing for up to 3 years, or accumulation of 10,000 patients. The primary outcome for this study will be "local and systemic allergic reactions resulting in hospitalization, emergency department care, or ambulatory visits that are associated with epinephrine injections (hereafter referred to as "serious allergic reactions"). They will be ascertained through diagnosis codes for anaphylaxis, anaphylactic reaction, anaphylactic shock, systemic allergic reaction, or upper airway obstruction.

- **b.** The objectives are as follows:
  - i. Estimate the incidence of serious allergic reactions in patients receiving GRASTEK resulting in hospitalization, emergency department care, or epinephrine injection in the ambulatory setting.
  - ii. Conduct a case series analysis of exposed patients who experience a serious allergic event to describe potential risk factors.
  - iii. Describe characteristics of patients initiating GRASTEK with respect to demographics, concomitant medications and co-morbidities.

c. The sponsor noted several limitations associated with the proposal:

i. Claims data will not capture new users during the initial treatment, which will usually be conducted via a starter pack (5-day pack) given to patients by the prescribing physician. As most serious allergic reactions would be expected to happen during these early treatments, this exclusion will limit the studies ability to measure an accurate incidence of serious allergic reactions in all patient exposures, and could bias the results as the remaining cohort will consist of patients who tolerated the early doses without allegic reactions.

ii. Claims data will capture patterns of treatment refills but will not capture interruption of day-to-day therapy.

iii. Self-administration of epinephrine in the community setting will not be captured with claims data.

iv. Medical charts may not be available for all patients with outcomes of interest.

d. Review Team recommendations

i. To address the most significant limitation (failure to capture early administrations), the review team recommended, via email 03/24/2014, that the sponsor conduct the study using an integrated health care provider with linkage to electronic medical record data, which would provide documentation of early (e.g., starter pack) administration to each patient. Additionally, the review team recommended that the sponsor conduct the study for a full three years regardless of the number of patients enrolled.

In response to these recommendations, the sponsor submitted a revised proposal via email on 03/26/2014.

6. Summary of Agreed Upon Study Proposal

a. In the revised proposal, the sponsor will conduct two sub-studies, one using the claims-based design as originally proposed, and one using an electronic medical record. The objectives for both studies will be the same as originally proposed. The integrated healthcare system will pick up the events that are associated with early exposures based on use of starter packs as well as events that might occur during exposure to longer term therapy. The claims database will offer a larger sample size to assess the incidence and risk factors for the longer term outcomes (i.e., those that occur after the starter pack exposure). Both studies will be conducted for a full three years, regardless of the number of patients enrolled.

b. Source population: The claims database is expected to represent 25-30 million patients. The EMR study will use an integrated healthcare provider as the source data, and is anticipated to represent less than 5 million patients. The sponsor notes that they will have to identify an integrated health system that: (1) utilizes sufficient amounts of this product in their system which is affected by

regional exposure to the antigens, and (2) is able to ascertain in-office exposures and administrations through starter packs.

c. Cohort Identification: The study will enroll all new users of GRASTEK based on dispensing claims (in the claims study) or EMR evidence of in-office administration or dispensing (EMR study). The studies will also capture exposures to other immunotherapies (e.g. beta-agonist or steroid inhalers).

d. Outcome: The primary outcome for the studies will be local and systemic allergic reactions resulting in hospitalization, emergency department care, or ambulatory visits that are associated with epinephrine injections (i.e., "serious allergic reactions"). They will be ascertained through diagnosis codes for anaphylaxis, anaphylactic reaction, anaphylactic shock, systemic allergic reaction, or upper airway obstruction. Outcomes will also be identified through codes for procedures to treat these conditions, such as emergency endotracheal intubation or surgical airway. Each outcome identified through automated data will be adjudicated by a panel of clinicians who are experts in the field using medical chart review.

e. Analysis Plan:

i. Determine incidence rate of the study outcome
ii. Describe demographic characteristics, important comorbidities and concomitant medications, including allergy immunotherapy and calendar month. The sponsor will also describe dispensing patterns of GRASTEK preceding the events, based on claims data, as well as any mention of treatment interruption or suspected allergic trigger documented in the medical record.
iii. Time at risk, which will be detailed in the protocol, will be calculated based on days' supply of medication plus a 7 day grace period after exposure ends. Sensitivity analyses will apply a 14 day period after exposure ends. A secondary analysis will limit the exposure to the first 30 days of drug use.
iv. There is no pre-specified sample size, however, based on commercial forecasts, the sponsor expects to enroll at least 10,000 new GRASTEK users.

f. Limitations: The limitations listed above still apply, however, the EMR study will help to ascertain risk of serious allergic reactions during early therapy.

g. Timelines: The sponsor anticipates submitting a full protocol by 31 JAN 2015 fo the claims based study and November 2015 for the EMR study. As this is a retrospective cohort study, patients available for the cohort will begin to accrue with product launch (anticipated Q2 2014), and data collection is anticipated to end three years later (Q2 2017), with a final study report to be submitted Q2 2018.

7. Recommendations

Based upon the submitted information and current clinical knowledge, at this time OBE/DE agrees that routine pharmacovigilance as proposed by the sponsor is appropriate should this product be licensed.

While limited by a relatively small size and lack of controlled comparison group, the post-market study to be conducted by the sponsor as a post-market commitment will provide further enhanced monitoring for serious allergic reactions.