



Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

Pharmacovigilance Plan Review Memorandum

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[Please note that Branch Chief has signed on behalf of Dr. Rohan.]

Through: Meghna Alimchandani, MD,
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To: Co-chairs:
CAPT Colleen Sweeney
Office of Vaccines Research and Review (OVR)

Subject: BLA 125592/0.62
Sponsor's response to February 6, 2017 telephone
conference clarifying the single PMC

Applicant: Merck Sharp & Dohme Corp.

Product: House Dust Mites (*Dermatophagoides farinae* and
Dermatophagoides pteronyssinus) Allergen Extract
Sublingual Tablet
12 SQ-HDM
(MK-8237)
Proposed Trade Name: ODACTRA™

Proposed Indication: As immunotherapy for the treatment of house dust mite
(HDM)-induced allergic rhinitis, with or without conjunctivitis,
confirmed by positive skin test or in vitro testing for
Dermatophagoides farinae or *Dermatophagoides*
pteronyssinus IgE antibodies. The product is approved for
use in adults 18 through 65 years of age.

Submission Date: 07-FEB-2017

PVP Submission
Date: 09-FEB-2016

Action Due Date: 08-FEB-2017

Addendum to OBE/DE Pharmacovigilance Plan Review

Background:

Per the February 6, 2017, teleconference between FDA and the sponsor regarding the proposed PMC for the above product, the following clarifications have been submitted:

A post-market electronic health record (EHR) study to further describe the safety profile of ODACTRA in marketed use in the United States:

The study will enroll all new users of ODACTRA identified through a large integrated electronic health records dataset. The study will aim to accrue 10,000 patients over a 5-year period. Annual accrual rates will be assessed at the end of each year and compared against projected rates. The sponsor will inform the agency if the rate of accrual is substantially lower than the projected rate and discuss the possibility of futility. The study will assess the first in-office exposure to ODACTRA and all subsequent exposures and outcomes (i.e. serious allergic reactions and eosinophilic esophagitis) to the extent that they are available within the EHR system.

Final protocol submission date: 6 months from approval date

Study completion date: February 28, 2024

Final report Submission date: February 28, 2025 (or one year after study completion date, whichever is later).

Protocol Synopsis:

Study Title: Post-Market Integrated Electronic Health Record (EHR) Based Study of Serious Allergic Reactions and Eosinophilic Esophagitis (EoE) in Marketed Use of ODACTRA™ in the United States (US)	
Background	According to the USPI, initial use of ODACTRA should occur under medical supervision due to the risk of serious allergic reactions to immunotherapy shortly after treatment initiation. In-office administration of ODACTRA cannot be assessed through claims data because there are no codes to document directly observed therapy with this agent. An integrated EHR system with a strong patient retention rate can reliably capture the initial use of ODACTRA and subsequent exposures and outcomes.
Objective(s)	Primary objective: To estimate the incidence of serious allergic reactions and EoE among patients exposed to ODACTRA using an integrated EHR database Secondary objectives: 1. To characterize the confirmed cases of serious allergic event and EoE in terms of their clinical characteristics, patient characteristics and attributes proximal to the time of the confirmed events. 2. To describe characteristics of patients initiating ODACTRA with respect to demographics, concomitant medications, and co-morbidities given available EHR data
Study Design	This prospective cohort study will use an integrated electronic health records (EHR) database to identify patients newly exposed to ODACTRA, identify potential cases of acute serious allergic reactions and EoE and compute incidence rates of these adverse events. Each patient enters the study cohort at the office visit in which the index exposure occurs and follow-up continues as long as the patient remains in the EHR system and until the data accrual period ends.
Study Population	All patients for whom new ODACTRA exposure is identified in the EHR database will be eligible for inclusion in the cohort.
Study Duration	The study will aim to accrue 10,000 patients over a 5 year period. Annual accrual rates will be assessed at the end of each year and compared against projected rates. A futility assessment will be conducted after 3 years and shared with the agency.
Exposure and Outcome	Exposure to ODACTRA will be identified using EHR fields indicating a new exposure to ODACTRA. Outcomes will include serious allergic reactions and EoE.
Statistical Methods	Patients treated with ODACTRA and patients experiencing events of interest will be described according to all available demographic characteristics, prescription medications, and comorbidities. Incidence rates of study outcomes will be described with 95% CIs.
Sample Size	A total of 10,000 patients are targeted for this EHR-based study. Using a health insurance claims database, the unadjudicated rate of serious allergic reactions and EoE in a population of patients receiving subcutaneous immunotherapy (SCIT) was 121/10,000 and 14/10,000 person years, respectively. Using worldwide post-marketing data from Grazax, the reporting rate of serious allergic reactions and EoE is 5.6/10,000 and 0.6/10,000 person years, respectively. Assuming the SCIT rates and 10,000 exposed patient years, the total number of expected cases of serious allergic reactions and EoE is 121 (95% CI = 100 – 145) and 14 (95% CI = 8-23), respectively. Assuming the Grazax rates and 10,000 exposed patient years, the total number of expected cases of serious allergic reactions and EoE is 6 (95% CI = 2-12) and 1(95% CI = 0-5), respectively.
Limitations	This study will aim to capture exposures that occur during the initial in-office visit and all subsequent exposures and outcomes that occur. Given the rarity of the study outcomes, we will be able to describe the incidence rates with limited precision, which will be reflected by the CIs of the incidence rates. The reliability for EHR data to capture subsequent exposures and outcomes (which may occur across various care settings with different EHRs) has not been established. However, in a large integrated EHR system with a strong patient retention rate, we anticipate good capture across settings. This study focuses on the period of time that is poorly captured in claims-based longitudinal analyses, which begin only with the dispensing of commercial product. It is expected that initial treatment with ODACTRA will occur using product samples dispensed by the prescribing physician.
Timelines	Final protocol submission date: 6 months from approval date Study completion date: February 28, 2024 Final report Submission date: February 28, 2025 (or one year after study completion date, whichever is later).

Pharmacovigilance Plan

1. Event-specific questionnaires to be used to follow-up reports of:

Important identified safety issues:

- Serious systemic allergic reactions, including anaphylactic reactions
- Local allergic reactions with potential to compromise airway
- Acute worsening of asthma symptoms (exacerbations)

Important potential safety issues

- Anaphylactic shock
- Eosinophilic esophagitis (EoE)

2. Periodic safety review on all spontaneous postmarketing adverse event reports including those related to important missing information:

- Pregnancy and lactation
- Use in children (<18 years of age)
- Use in elderly (> 65 years of age)
- Use in severe, unstable or uncontrolled asthma
- Co-administration with other SLIT products

3. A PMC study entitled: Post-Market Integrated Electronic Health Record (EHR) Based Study of Serious Allergic Reactions and Eosinophilic Esophagitis (EoE) in Marketed Use of ODACTRA in the United States (US)

REVIEW COMMENTS:

DE agrees that the sponsor proposed postmarket pharmacovigilance plan is acceptable should this product be licensed for use in adults 18-65 years of age. DE will review the protocol for the PMC study upon submission.