Summary Basis for Regulatory Action

Date: March 1, 2017

From: Colleen Sweeney, R.N., M.S., Chair of the Review Committee

BLA/STN#: 125592/0

Applicant Name: Merck Sharp & Dohme Corporation (Corp.), a subsidiary of Merck & Company (Co.), Incorporated (Inc.) [Merck]

Date of Submission: February 9, 2016

Review Goal Date: February 8, 2017

Proprietary Name: ODACTRA™

Established Name: House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract

Indication and Usage:

ODACTRA is an allergen extract indicated as immunotherapy for house dust mite-(HDM)-induced allergic rhinitis, with or without conjunctivitis, confirmed by *in vitro* testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites, or skin testing to licensed house dust mite allergen extracts. ODACTRA is approved for use in persons 18 through 65 years of age.

Dosage Form: Tablet for sublingual use

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority: Marion F. Gruber, Ph.D., Director, Office of Vaccines Research and Review

x I concur with the summary review.
□ I concur with the summary review and include a separate review to add further analysis.
□ I do not concur with the summary review and include a separate review.

Material Reviewed/ Consulted Specific documentation used in developing the SBRA	Reviewer Name – Document(s) Date
Clinical Review	Kathleen Hise, M.D. – February 24, 2017
Clinical Statistical Review	Zhong Gao, Ph.D. – December 15, 2016 Elizabeth Teeple, Ph.D. – January 15, 2017
CMC Review	Taruna Khurana, Ph.D. – January 10, 2017
Microbiological Testing Review	Hyesuk Hong, Ph.D. – January 25, 2017
Toxicology Review	Nabil Al-Humadi, Ph.D. – December 16, 2016 Ching-Long Joseph Sun, Ph.D. – December 16, 2016
Bioresearch Monitoring Review	Colonious King, CSO – January 11, 2017
Facilities and CMC Review	Joyce Rockwell – January 24, 2017
Pharmacovigilance Review	Patricia Rohan, M.D. – January 26, 2017
Advertising and Promotional Labeling Proprietary Name Review	Oluchi Elekwachi, Pharm.D., MPH – January 4, 2017 Oluchi Elekwachi, Pharm.D., MPH - March 10, 2016
Approved Draft Labeling	February 28, 2017

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1. Introduction

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck) submitted a Biologics License Application (BLA), STN 125592, for licensure of House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract. The proprietary name is ODACTRA™ and the dosage form for this product is a tablet for sublingual use. ODACTRA is an allergen extract indicated as immunotherapy for house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis, confirmed by *in vitro* testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites, or skin testing to licensed house dust mite allergen extracts. ODACTRA is approved for use in adults 18 through 65 years of age.

ODACTRA is a freeze dried tablet formulation of HDM allergen extracts from *Dermatophagoides farinae (Der far)* and *Dermatophagoides pteronyssinus (Der pte)* for sublingual use. ODACTRA tablets are to be placed under the tongue until dissolution. The recommended dose of ODACTRA is one sublingual tablet daily. The first dose should only be administered in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. The patient should be observed for 30 minutes after receipt of the first dose.

ODACTRA tablets are presented in labeled blister packages containing 10 single tablet doses each for patient self-administration. Labeling includes a Boxed Warning and a Medication Guide, both of which emphasize the potential risk for severe allergic reactions and access to auto-injectable epinephrine.

2. Background

Allergic rhinoconjunctivitis (ARC) affects over 500 million persons worldwide, including approximately 30 million persons in North America. Dust mites are one of the most common causes of perennial allergies. While allergen avoidance and pharmacotherapy can provide relief, for many persons symptoms remain. For some of these patients allergen immunotherapy is a reasonable alternative. Subcutaneous allergen immunotherapy (SCIT) has been practiced since the early 20th century. The administration of allergen extracts orally or sublingually is a more recent development. At this time, there are three United States (U.S.) licensed seasonal pollen allergen extract products for sublingual allergen immunotherapy (SLIT). ODACTRA would be the first approved perennial allergen extract in the U.S. for SLIT.

Dust mites belong to the taxonomic (phylogenetic) family *Acaridae* and subfamily *Pyroglyphidae*. The most common genus of mites found in North America and Europe is *Dermatophagoides* of which there are two species: *Der far* and *Der pte*. The HDM is globally ubiquitous in human habitats and a significant cause of allergic rhinoconjunctivitis and allergic asthma, making it one of the most important perennial allergens worldwide. Estimates regarding the

prevalence of HDM allergy vary widely depending on diagnostic tools used. The prevalence of sensitization to *Der far* and *Der pte* varies by geographic location and by age, with the lowest prevalence of HDM associated atopy and asthma in children less than 5 years of age.

3. Clinical/Statistical

a) Clinical Program

On March 7, 2012, the Applicant submitted U.S. Investigational New Drug (IND) 15015 to the Center for Biologics Evaluation and Research (CBER). Several meetings and discussions were held with the Applicant under the IND. Issues that were resolved under the IND included the analytical method to define potency of ODACTRA. In addition, the design of the pivotal safety and efficacy study was discussed related to dose selection, subject population, safety endpoints and the predefined statistical criteria for demonstration of efficacy.

Prior to the IND submission, issues related to defining clinical efficacy of future allergenic products were discussed with the Allergenic Products Advisory Committee (APAC) on May 12, 2011. Specifically, the Food and Drug Administration (FDA) discussed with the APAC the potential use of environmental exposure chambers (EECs) to assess efficacy in clinical studies. EECs are self-contained units with controlled air that expose patients to specific and quantifiable amounts of allergens, such as house dust mites. The FDA provided background information on the advantages and disadvantages of natural exposure studies for allergens and the potential use of EECs to better control for variability. The APAC discussed the challenges of designing a controlled environmental study of sufficient size. The APAC recommended that while there was not sufficient experience with EECs to determine their relative utility in establishing efficacy, they may be useful as a complement to natural exposure clinical studies. The Applicant performed one Phase 2 study under U.S. IND 15015 using an EEC to assess safety and efficacy of the product in adult subjects.

Also discussed at this APAC meeting in 2011 were statistical considerations for the design and interpretation of Phase 3 clinical studies of allergenic products. FDA presented an overview of basic statistical concepts that the Agency applies to the review of studies of allergenic products. Different statistical concepts and their application to Phase 3 studies of allergenic products were discussed including covariates, clinically meaningful differences, and the appropriate timeframes for performing studies with respect to allergy seasons. In particular, FDA emphasized that the lower bound of the 95-percent confidence interval (CI) between the treatment and control group should be greater than a pre-specified threshold to ensure that a statistically significant difference translates into a clinically meaningful difference.

The Applicant submitted the BLA on February 9, 2016. Data from 8 clinical studies were provided. The demonstration of efficacy for U.S. licensure of ODACTRA was based on 3 of these studies: a Phase 2 EEC study (P003), and two Phase 3 field

efficacy studies (P001 and P015). Subjects in all 3 of these studies had a history of symptomatic allergic rhinitis with or without conjunctivitis and with or without asthma and were sensitized to *Der far* and/or *Der pte* as determined by HDM-specific IgE and skin prick test response to *Der far* and/or *Der pte*. Data from all 8 clinical studies were evaluated to establish safety of the product. However, the pivotal safety database was derived from 4 of these 8 clinical studies: P001, P003, P015, and P014.

Overview of Clinical Efficacy Study Results

The 3 studies that contributed to the efficacy data to support U.S. licensure of ODACTRA are summarized below:

Study P001 (North American Field Efficacy Study; NCT01700192)

This Phase 3 double-blind, randomized, placebo-controlled field efficacy study was conducted in the U.S. and Canada from January 24, 2013 to April 27, 2015. The primary objective of the study was to evaluate the efficacy and safety of ODACTRA compared to placebo in the treatment of HDM-induced allergic rhinitis with or without conjunctivitis, with or without asthma. One thousand four hundred eighty two (1482) adolescent and adult subjects 12 years of age and older were randomized 1:1 to receive either ODACTRA 12 SQ-HDM(n=741) or placebo (n=741) once daily for 52 weeks. Please refer to Section 4a for the definition of SQ-HDM.

The primary efficacy endpoint was defined as the difference in the average total combined rhinitis score (TCRS) between treatment and placebo groups during the last 8 weeks of treatment. The efficacy of ODACTRA was assessed through self-reporting of symptoms and medication use. Based on these self-assessments, the TCRS, daily symptom scores (DSS) and daily medication scores (DMS) for rhinoconjunctivitis were calculated. Daily symptoms included four nasal symptoms (runny nose, stuffy nose, sneezing, and itchy nose) and two ocular symptoms (gritty/itchy eyes and watery eyes). Each of these symptoms was individually graded by subjects daily on a scale of 0 (none) to 3 (severe) and then summed. Subjects in active and placebo arms of this study were allowed to take symptom-relieving allergy medications (including oral and ocular antihistamines and nasal corticosteroids) during the study as needed. The DMS measured the use of these standard symptom-relieving allergy medications. Predefined daily maximum scores were assigned to each class of rhinitis and conjunctivitis medication as 0=none, 6=oral antihistamine, 6=ocular antihistamine, and 8=nasal corticosteroid.

The pre-specified success criteria for efficacy were demonstration of a point estimate difference between treatment and placebo of ≤-15% and an upper bound of the 95% CI of that difference of ≤ -10%. The relative treatment difference based on the average TCRS during the last 8 weeks of treatment was -17.2% (95% CI, -25.0%, -9.7%).

Study P015 (European Field Efficacy Study; NCT01454544)
This Phase 3 double-blind, randomized, placebo-controlled, field efficacy study was conducted in Europe from October 27, 2011 to April 4, 2013. The primary objective of the study was to assess the efficacy and safety of ODACTRA in adults 18 through 65 years of age with HDM-induced allergic rhinitis with or without conjunctivitis with or without asthma. Nine hundred ninety two (992) adult subjects were randomized 1:1:1 to receive either placebo (n=338), ODACTRA 6 SQ-HDM (n=336) or ODACTRA 12 SQ-HDM (n=318) for 52 weeks.

The primary efficacy endpoint was the treatment difference relative to placebo of the average TCRS during the last 8 weeks of treatment. This study was not conducted under U.S. IND and no pre-specified criteria for success were defined. The relative treatment difference between the placebo and ODACTRA 12 SQ-HDM in the average TCRS during the last 8 weeks of treatment was -16.1% (95%CI, -27.8%, -5.7%).

Study P003 (Environmental Exposure Chamber Study; NCT01644617)
This Phase 2 double-blind, randomized, placebo-controlled study was conducted at a single site in Austria from October 29, 2012 to August 27, 2013.

The primary objective of the study was to evaluate the efficacy and safety of ODACTRA compared to placebo in the treatment of HDM-induced rhinitis following challenge in an EEC. One hundred twenty four (124) adult subjects 18 years of age and older with HDM-induced rhinitis with or without conjunctivitis with or without asthma were randomized 1:1:1 to receive either placebo (n=41), ODACTRA 6 SQ-HDM (n=41), or ODACTRA 12 SQ-HDM (n=42). Subjects received daily dosing with ODACTRA or placebo for 24 weeks prior to a 6 hour challenge in an EEC with a continuous high concentration of HDM allergen (approximately 0.3 grams HDM allergen mixture containing 10:10:1 *Der far* whole bodies, *Der pte* whole bodies, and feces from both species), which reflects the composition of mite material during natural exposure. Prior to the challenge sessions, subjects were required to stop their medications to treat allergic rhinitis and conjunctivitis symptoms but were allowed to use rescue medications while in the EEC. Each session was monitored and subjects were provided medical treatment if warranted. While in the EEC, subjects recorded the presence of nasal symptoms (itchy nose, blocked nose, runny nose, and sneezing) every 15 minutes in electronic diaries. Scores were assigned for each symptom based on a 4-point rating scale (0=none to 3=severe) and summed in order to calculate the total nasal symptom score (TNSS). The primary efficacy endpoint was to evaluate the difference in the average TNSS between treatment and placebo group during the chamber session at Week 24. No pre-specified criteria for success were defined. The treatment difference between ODACTRA 12 SQ-HDM and placebo was -48.6% (95% CI:-60.2%, -35.3%).

Summary of Clinical Efficacy
Together, the results from the two Phase 3 field efficacy studies P001 and P015 and the Phase 2 EEC study P003 demonstrate efficacy of ODACTRA in the treatment of HDM-induced allergic rhinitis, with or without conjunctivitis. Data from studies P001 and P015 demonstrate a reduction in TCRS during the last 8 weeks of a 52

week treatment course with ODACTRA. In study P001, conducted in adolescents and adults in the U.S. and Canada, the pre-specified criterion for success of ≤-15% for the difference in average TCRS between treatment and placebo was met, even though the lower bound of the 95% CI for the difference (i.e. -9.7%) was slightly above the pre-specified criterion of -10%. Furthermore, results from study P015 conducted in adults 18 years of age and older showed the treatment difference between placebo and ODACTRA 12 SQ-HDM in the average TCRS during the last 8 weeks of treatment was -16.1% (95% CI, -25.8%, -5.7%). It should be noted that in these field studies, there is no comparison between pre-season and post-season effects. In addition, allergen exposure in the field can vary due to a number of environmental factors. Furthermore, subjects are generally sensitized to more than one allergen. Consequently, a substantial change in response to immunotherapy for perennial allergens such as HDM is not expected in field studies. However, the results of the Phase 2 EEC study P003 performed in adults 18 years of age and older provide robust supportive data regarding the efficacy of ODACTRA. In this study, the treatment difference relative to placebo in the average TNSS at Week 24 was -48.6% (95% CI:-60.2%, -35.3%) in the 12 SQ-HDM group.

The number of adolescents 12 through 17 years of age included in study P001 was too small (n=189), to support a labeled indication for this age group at this time.

Bioresearch Monitoring
During review of the BLA two domestic sites from trial P001 were inspected under the Agency's Bioresearch Monitoring program. The results of these Bioresearch Monitoring inspections of study protocol P001 at the two clinical sites did not reveal problems that impact the data submitted to this BLA.

b) Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), this application was required to contain an assessment of the safety and effectiveness of the product for the claimed indication in all pediatric age groups unless the requirement is waived, deferred, or inapplicable. The Applicant submitted a pediatric plan on February 9, 2016, with a request for a partial waiver from the requirements of PREA for children less than 5 years of age and a deferral for studies in children 5 through 17 years of age. On November 12, 2016, Merck's pediatric plan was presented to the Pediatric Review Committee (PeRC), who agreed with CBER's decision to grant the following:

- The pediatric study requirement in children less than 5 years of age for the proposed indication was waived since necessary studies are impossible or highly impracticable. This is because the number of children younger than 5 years of age with allergic rhinitis/rhinoconjunctivitis with confirmed sensitivity to HDM *Der far* or *Der pte* is too small.

- The pediatric study requirement in children 5 through 17 years of age for the proposed indication was deferred because the product is ready for approval for use in adults before pediatric studies are complete.

The Applicant agreed to the following PREA required deferred pediatric studies to evaluate the safety and efficacy of ODACTRA as immunotherapy for diagnosed HDM-induced allergic rhinitis, with or without conjunctivitis, in children 5 through 17 years of age:

1. Deferred pediatric study to evaluate the safety and efficacy of ODACTRA in pediatric subjects 5 through 17 years of age with HDM-induced allergenic rhinitis/rhinoconjunctivitis with or without asthma.

   Final Protocol Submission: October 1, 2017

   Study Completion Date: July 1, 2021

   Final Report Submission: July 1, 2022

2. Deferred pediatric study to evaluate safety of ODACTRA in pediatric subjects 5 through 17 years of age with HDM-induced allergenic rhinitis/rhinoconjunctivitis with or without asthma.

   Final Protocol Submission: October 1, 2017

   Study Completion Date: July 1, 2021

   Final Report Submission: July 1, 2022

4. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

Product Description

ODACTRA is comprised of two separate drug substances consisting of allergen extracts from house dust mites *Der far* and *Der pte* (b) (4) . ODACTRA is a white to off-white, circular sublingual tablet with a debossed pentagon detail on one side. ODACTRA is available in a single strength tablet of 12 SQ-HDM. ODACTRA is a freeze-dried tablet that also contains fish gelatin National Formulary (NF) mannitol, United States Pharmacopeia (USP), and sodium hydroxide (NF), as inactive ingredients.

The development unit (DU) is the biological potency unit used by the Applicant in the clinical studies provided in the BLA. The DU is determined at the (b) (4) The sum of 0.5 DU of

Der far and 0.5 DU of *Der pte* is equal to 1.0 DU in the HDM product. The potency of HDM tablets for commercial use is designated as 12 SQ-HDM, where SQ designates the method of standardization based on biological potency, major allergen content, and complexity of the allergen extract. The terms SQ-HDM and DU are equivalent. The (b) (4) analytical procedure is a quantitative (b) (4) assay developed by the applicant and is used as the lot release potency test for determination of the (b) (4) of drug product (DP). The lot release acceptance criterion is (b) (4) of the stated amount. The stated amount is 12 SQ-HDM.

Product Composition

The composition of the ODACTRA final drug product (DP) tablets and the function of the ingredients in the DP tablets are provided in Table 1 below.

Table 1: Quantitative Composition of ODACTRA Tablet, 12 SQ-HDM

Ingredient	Quality Standard	Function	Amount per Tablet
House Dust Mite Allergen Extract Drug Substance	In House	Active ingredient	12 SQ-HDM[a]
Gelatin (Fish, (b) (4)	NF	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Mannitol	USP	(b) (4)	(b) (4)
Sodium Hydroxide	NF	(b) (4)	(b) (4)
Purified Water	(b) (4)	Vehicle	(b) (4)
(b) (4)			(b) (4)
(b) (4)			(b) (4)

(b) (4)

Presentation and Packaging System
ODACTRA tablets are packaged in aluminum blister cards, each containing 10 tablets, and supplied in cartons containing three blister cards each for a total of 30 tablets per carton.

Manufacturing Overview
The manufacturing of ODACTRA begins (b) (4)

Drug Substance
The DS is manufactured (b) (4)

The DS manufacturing process begins by (b) (4)

(b) (4)
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(b) (4)

(b) (4)

Primary stability studies on three batches of the DS were performed in support of the storage time for the DS and to confirm the appropriate specifications for the DS throughout the expiry period. The dating period of the DS is (b) (4) from the date of manufacture of the DS when stored at (b) (4)

The applicant performed manufacturing process development and process validation, analytical methods development and validation. Stability studies were performed to establish the suitability for the DS. The specific release criteria developed for the DS are acceptable to demonstrate suitability for intended use.

Drug Product

ODACTRA tablets are manufactured as a dissolving formulation using (b) (4) Steps in the manufacture of ODACTRA DP by Catalent Pharma Solutions Ltd., include (b) (4) , freeze drying, and sealing of tablets in blister cards (one tablet is packed per cavity and there are 10 tablets per blister card). The sealed blister cards of freeze dried tablets are then shipped to Merck Sharp and Dhome Corp. in (b) (4) for secondary packaging.

The commercial batch size of DP is (b) (4) Three process performance qualification (PPQ) batches were manufactured for process validation and evaluation. All lots met the release and shelf life specifications.

The primary CMC review issue that was raised and resolved during the review of the BLA concerns validation and system suitability criteria of the Applicant's (b) (4) method. The method is used as an alternative to the CBER lot release potency test for the allergenic activity of the final product. The Applicant submitted the full validation report for the (b) (4) assay conducted in accordance with the principles described in the International Council for Harmonization (ICH) guideline Q2(R1) "Validation of Analytical Procedures: Text and Methodology." The defined parameters were found acceptable. The Applicant also submitted trending and tracking data from multiple (b) (4) runs. Additional potency data was also provided from the (b) (4) assays performed after completion of the validation study. The additional data provided supported the current system suitability criteria.

The Applicant proposed a shelf life of 36 months from the date of manufacture of the DP for storage at (b) (4) controlled room temperature (25°C (b) (4) Stability studies were performed on three primary batches produced using the commercial process at commercial scale and process validation batches in support of the storage time for the DP and to confirm the appropriate specifications for the DS throughout the expiry period. The stability studies were conducted as per ICH guideline Q5C, and the data obtained support 36 months of shelf life of ODACTRA when stored at the recommended storage condition.

Container Closure System
The drug product is filled and lyophilized in an all-aluminum blister. The blister material consists of a (b) (4) blister material, (b) (4) paper/foil laminate lidding foil. The blister film is supplied by (b) (4) and the lidding foil is supplied by (b) (4) . Each blister card consists of one tablet per cavity with 10 tablets per blister card. Catalent Pharma Solutions Ltd. conducted the container closure integrity testing at the Wiltshire, UK, facility, employing the the (b) (4) . All acceptance criteria were met.

a) CBER Lot Release

The lot release protocol (LRP) template for the final DP was submitted to CBER for review and found acceptable after revisions. Tablet samples from the three DP process performance qualification (PPQ) lots were submitted to CBER's Laboratory of Immunobiochemistry (LIB) for qualification of the applicant's (b) (4) potency method. The tablet samples were tested in multiple (b) (4) runs and were within release acceptance criteria.

The final blister packaged tablet DP will be released by CBER. For routine lot release, the applicant will submit samples and a LRP for each final DP blister pack lots to CBER.

A lot testing plan was developed by the Division of Bacterial Parasitic and Allergenic Products (DBPAP), the Division of Manufacturing and Product Quality (DMPQ), and the Division of Biological Standards and Quality Control (DBSQC) and was found acceptable.

b) Facilities Review/Inspection

Facilities Review/Inspection
Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of ODACTRA are listed in Table 2 below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Table 2: Manufacturing Facilities Table for ODACTRA

Name/address	FEI number	DUNS number	Inspection/ waiver	Results/ Justification
Drug Product Manufacturing, primary packaging and labeling, and testing Catalent Pharma Solutions Ltd. Frankland Road Blagrove, Swindon, Wiltshire, SN5 8RU United Kingdom	3003812585	237676320	Waived	Team Biologics August/September 2016 Voluntary action indicated (VAI)
Drug Substance Manufacturing, testing, and release Drug Product Testing (b) (4)	(b) (4)		Pre-license Inspection	CBER (b) (4) No action indicated (NAI) Team Biologics (b) (4) Official action indicated (OAI)
Drug Product Release testing (b) (4)			Waived	ORA (b) (4) VAI

The (b) (4), Team Biologics inspection of (b) (4) was OAI and resulted in the issuance of an untitled letter on (b) (4). All of the issues that affect ODACTRA have been resolved.

A pre-license inspection of (b) (4), was conducted by CBER from (b) (4) for DS manufacturing and testing, DP testing, and stability testing. There were no inspectional observations noted during the inspection and the inspection was classified as NAI.

A pre-license inspection was waived for the manufacture of the drug product. Team Biologics conducted a surveillance inspection of Catalent Pharma Solutions Ltd., from August 30 through September 6, 2016. The

inspection was classified as VAI. Responses to the 483 observations were received and all inspectional issues were resolved.

A pre-license inspection was waived for a contract testing laboratory used as a back-up facility to perform certain release tests. Office of Regulatory Affairs (ORA) conducted a surveillance inspection of (b) (4) The inspection was classified as VAI. Responses to the noted observations on Form 483 were received and all issues were resolved.

c) Environmental assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

5. Nonclinical Pharmacology/Toxicology

The following non-clinical toxicity studies were conducted in order to identify and evaluate toxicity findings following the administration of ODACTRA DS:

Repeat-Dose Toxicity
A 26 week repeated, daily dose toxicity study was performed in mice incorporating a 4 week recovery period. Twenty four animals were dosed daily with the DS at levels of 0.9, 3.5 or 14 DU/day or vehicle (distilled water). No effects of treatment were observed including local reactions at the site of administration.

Genotoxicity
ODACTRA DS extracts were evaluated in various tests for genotoxicity including the following: bacterial reverse mutation (Ames) assays, an *in vivo* combination Comet assay with a rat bone marrow micronucleus test and an *in vitro* chromosome aberration study using human peripheral blood lymphocytes. No evidence of genotoxicity was observed in these studies with or without (b) (4) microsomes (S9) with the exception of the chromosomal aberration assay. In the chromosome aberration study, the DS did not induce structural chromosome aberrations following a 3 hour (hr) treatment and 17 hr recovery with or without S9 but did induce aberrations following a 20-hr treatment in the absence of metabolic activation. The genotoxic effect was accompanied by some suppression of mitotic index. However, the suppression of mitotic activity did not exceed the recommended limit as stated in various regulatory guidelines.

Reproductive and Developmental Toxicity

In embryo fetal development studies in mice, ODACTRA DS was administered subcutaneously from gestation days 6 to 17 (day of implantation inclusive through late gestation) at doses from 225 to 1800 DU/kg. The control animals were given the vehicle (purified water) alone. ODACTRA DS had no maternal effects or effects on embryo-fetal developmental toxicity except as noted below. Nonclinical assessments of perinatal and postnatal development have not been conducted.

A skeletal anomaly was observed in fetuses in the high dose group (50 DU/animal). Two of 105 fetuses (1.9% or 2/18 litters) in the control group and 4 of 104 fetuses (3.9% or 4/18 litters) in the high dose group had fused sternebrae. The upper limit of the historical data for this anomaly is 2/140 fetuses or 1.4% in 4 studies that were conducted at the test facility between the years 2003-2013. In assessing the finding, the BLA review committee considered the following: 1) No other embryonic abnormality was observed that would indicate a dysfunction in skeletal development; 2) The historical data for this anomaly were not based on a robust database with narrow confidence intervals and; 3). Use of subcutaneous immunotherapy with HDM allergen extracts in subjects including pregnant women supports the safety of this product. Therefore, it was concluded that the isolated finding of fused sternebrae in a single murine study did not represent a safety signal and would not be included in Section 8.1 of the package insert.

Local Toxicity

ODACTRA DP (tablet) was sublingually administered once a day for 7 days to rabbits at 12 and 24 DU/animal/day to determine local irritation to the buccal mucosa. No abnormal clinical signs, body weights changes, signs of irritation were observed on the buccal mucosa. No abnormal gross and histopathological findings were found.

6. Clinical Pharmacology

The mechanisms of action of sublingual allergen immunotherapy are not known.

7. Safety

Overview of Clinical Safety

Data from 4 double-blind, placebo-controlled randomized clinical studies (studies P001, P003, P015 and P014) provided information on the rates of serious adverse events (SAEs) and deaths in 1279 ODACTRA recipients and 1277 placebo recipients 18 through 65 years of age. SAE's were reported by 1.3% (16/1279) of ODACTRA recipients and by 1.8% (23/1277) of placebo recipients. No deaths were reported.

Study P001 was the only study designed to obtain data on solicited adverse reactions (ARs) during the first 28 days of treatment. Study P001 was a randomized, double-blind, placebo-controlled study conducted in the U.S. and Canada evaluating ODACTRA 12 SQ-HDM in subjects 12 years of age and older with HDM-induced allergic rhinitis with or without conjunctivitis. The safety analysis was based on the number of randomized subjects who received at least 1 dose of study drug (n=1482). Of these 1482 subjects, 640 subjects 18 through 65 years of age received at least one dose of ODACTRA and 631 subjects received placebo. The median treatment duration for subjects who received ODACTRA was 267 days (range 1 to 368 days). Study participants were provided side effect report cards in which they recorded the occurrence of solicited ARs daily for the first 28 days following treatment initiation.

The most common solicited ARs reported in in ≥10% of subjects treated with ODACTRA were: throat irritation/tickle (67%), itching in the mouth (61%), itching in the ear (52%), swelling of the uvula/back of the mouth (20%), swelling of the lips (18%), and swelling of the tongue (16%), throat swelling (14%), nausea (14%), tongue pain (14%), tongue ulcer/sore on the tongue (12%), stomach pain (11%), mouth ulcer/sore on the mouth (10%) and taste alteration (10%). Less than 1% of these ARs were severe. Participants were monitored for unsolicited adverse events (AEs) and serious adverse events (SAEs) for the duration of therapy (up to 52 weeks). The following unsolicited AEs were reported in numerically more subjects treated with ODACTRA than with placebo and occurred in ≥1% of subjects 18 through 65 years of age within 28 days after initiation of treatment with ODACTRA: oral paresthesia (9.2% vs. 3.2%), tongue pruritus (4.7% vs. 1.1%), oral pain (2.7% vs. 0.6%), stomatitis (2.5% vs. 1.1%), dyspepsia (2.2% vs. 0.0%), pharyngeal erythema (2.0% vs. 0.3%), eye pruritus (1.7% vs. 1.4%), oral mucosal erythema (1.7% vs. 0.2%), upper respiratory tract infection (1.6% vs. 1.1%), sneezing (1.6% vs. 0.3%), lip pruritus (1.4% vs. 0.3%), dysphagia (1.4% vs. 0.0%), fatigue (1.3% vs. 1.0%), hypoesthesia oral (1.3% vs. 1.0%), oropharyngeal pain (1.3% vs. 0.6%), chest discomfort (1.3% vs. 0.3%), dry throat (1.3% vs. 0.3%), pruritus (1.1% vs. 1.0%), and urticaria (1.1% vs. 0.3%). One case of eosinophilic esophagitis (EoE) was diagnosed in an ODACTRA recipient on Day 204 of treatment confirmed by biopsy which resolved with treatment. No cases of confirmed EoE occurred in the placebo group. The percentage of all enrolled subjects who dropped out of the study was higher in the ODACTRA group (24.2%) compared to the placebo group (17.3%). The rates of SAEs were 1.5% in the ODACTRA group compared to 0.9% in the placebo group. A causal relationship between these SAEs and ODACTRA was not established. No deaths were reported.

Safety data pertaining to the frequencies of unsolicited AEs and SAEs in ODACTRA and placebo recipients enrolled in studies P003, P014 and

P015 were consistent with data obtained from P001. Based on data from 8 clinical trials conducted with different doses of ODACTRA, EoE was reported by 2 out of 2737 ODACTRA recipients (0.07%) compared to 0 out of 1636 placebo recipients (0%).

Summary of Clinical Safety

The data provided in the BLA support the safety of the 12 SQ-HDM dose of ODACTRA in adults 18 through 65 years of age. Although ODACTRA is commonly associated with ARs such as throat irritation/tickle, itching in the mouth, itching in the ear, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, nausea, tongue pain, throat swelling, tongue ulcer/sore on the tongue, stomach pain, mouth ulcer/sore on the mouth and taste alteration, less than 1% of these ARs were severe.

Based on the safety data from 1279 subjects across 4 clinical studies who received ODACTRA for up to 52 weeks, the rates of anaphylaxis, EoE and symptoms requiring use of epinephrine were less than 1% for each of these outcomes. No deaths occurred.

EoE has been reported in subjects taking ODACTRA and patients who have been prescribed licensed SLIT products. Therefore, the package insert lists EoE under Section 5 Warnings and Precautions.

Although the occurrence of anaphylaxis or systemic allergic reactions observed in clinical studies pre-licensure was not common, treatment with ODACTRA may require use of epinephrine. For this reason, the product labeling includes a Black Box Warning and a Medication Guide, both of which emphasize the risk of severe allergic reactions and need for access to auto injectable epinephrine.

The applicant will conduct a post-marketing study under 21CFR601.70 to further describe the safety profile of ODACTRA with respect to EoE and systemic allergic reactions. (Please see Section 9.)

The total number of adolescents 12 through 17 years of age (n=94) and adults > 65 years of age (n=11) enrolled in the pivotal studies who received ODACTRA was too small to support the safety of the product in these age groups at this time.

8. Advisory Committee Meeting

The application was not referred to the Allergenic Product Advisory Committee (APAC) because our review of information submitted in the BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

9. Other Relevant Regulatory Issues

Post Marketing Commitment Studies

The BLA contained two proposed post marketing commitment (PMC) studies subject to 21 CFR 601.70, to further describe the safety profile of ODACTRA in marketed use in the US. These studies were a claims-based study and an electronic health record (EHR) study intended to estimate the incidence of serious allergic reactions and EoE. Both studies would enroll all new users of ODACTRA for a period of at least three years and until at least 3,000 patients were accrued between both PMCs.

CBER identified the following limitations of the applicant's proposal:

- The proposed studies had inadequate statistical power to evaluate the occurrence of EoE.
- Claims data may not adequately capture events of interest, particularly EoE.
- As proposed, the EHR study was designed to evaluate only the first dose of ODACTRA, and thus not useful in capturing EoE and other events with later onset.

According to CBER's recommendations, the applicant committed to conduct one EHR study (instead of the 2 studies originally proposed) that will enroll all new users of ODACTRA identified through a large integrated EHR dataset that will assess the first in-office exposure to ODACTRA and all subsequent exposures and outcomes (e.g., serious allergic reactions and EoE). The study will aim to accrue 10,000 patients over a 5-year period. Annual accrual rates at the end of each year will be assessed and compared against projected rates. The revised concept protocol was submitted to the BLA on February 8, 2017. Dates of the final protocol submission, study completion and final report submission were included in the revised protocol and deemed acceptable.

10. Labeling

Proposed Proprietary Name

The proposed proprietary name, ODACTRA, was found acceptable by the Advertising and Promotional Labeling Branch (APLB) on March 10, 2016. OVRR communicated the acceptability of the proprietary name to the applicant on March 31, 2016.

On January 4, 2017, APLB reviewed the package insert, medication guide, and carton and container labels, from a promotional and comprehension perspective. APLB had minor comments, which were resolved in an acceptable manner.

Package Insert (PI)
ODACTRA is a product for which patient labeling could help prevent SAEs including anaphylaxis and EoE and inform the patient of serious risks relative to benefit that could affect their decisions to use, or continue to use, the product. A Black Box Warning has been included in the PI to address the risk of systemic allergic reactions including anaphylaxis which may be life threatening and the need for access to auto-injectable epinephrine.

All issues pertaining to the PI were resolved in an acceptable manner following discussions between CBER and the applicant.

Medication Guide
As per 21 CFR Part 208, this product poses a serious and significant public health concern requiring the distribution of a Medication Guide.

All issues pertaining to the medication guide were resolved in an acceptable manner following discussions between CBER and the applicant.

Carton and Container Labeling
The carton and container labels are in compliance with 21 CFR 610.61 through 21 CFR 610.67 and 21 CFR 207.35. All issues pertaining to the carton and container labeling were resolved in an acceptable manner following discussions between CBER and the applicant.

11. Recommendations and Risk/Benefit Assessment

a) Recommended Regulatory Action

The review committee recommends approval of this product for licensure.

b) Risk/Benefit Assessment

The data submitted to this BLA support the clinical effectiveness of ODACTRA for the treatment of HDM induced allergic rhinitis, with or without conjunctivitis, in adults 18 through 65 years of age with confirmed HDM allergy.

Data from two Phase 3 field efficacy studies, P001 and P015, and one EEC study, P003, demonstrate the effectiveness of ODACTRA for the treatment of HDM-induced allergic rhinitis, with or without conjunctivitis in adults 18 through 65 years of age with confirmed HDM allergy based on HDM specific IgE and skin prick testing. These data demonstrate that ODACTRA when administered daily for approximately 52 weeks is associated with a reduction in allergic symptoms (rhinitis with or without conjunctivitis) and medication use.

Data from study P003 demonstrate a substantial reduction in nasal symptoms as early as 24 weeks after initiation of therapy.

Based on data from 1279 adults 18 through 65 years of age who received at least one dose of ODACTRA, the product is associated with ARs such as throat irritation/tickle, itching in the mouth, itching in the ear, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, throat swelling, nausea, tongue pain, throat swelling, tongue ulcer/sore on the tongue, stomach pain, mouth ulcer/sore on the tongue, and taste alteration during the first 28 days of treatment. Less than 1% of these reactions were severe. The estimated rates of outcomes such as anaphylaxis, EoE and symptoms requiring use of epinephrine were less than 1% for each of these outcomes.

Taken together, these data support a favorable risk-benefit assessment of ODACTRA for use in persons 18 through 65 years of age with confirmed HDM induced allergic rhinitis with or without conjunctivitis.

c) Recommendation for Postmarketing Risk Management Activities

There was no recommendation for postmarketing risk management activities.

d) Recommendation for Postmarketing Activities

Merck will conduct a deferred required postmarking pediatric study under PREA as required by Section 505b(a) of the Food Drug and Cosmetic Act (FDCA), as described above in Section 6.

In addition to routine pharmacovigilance, the applicant will conduct one postmarketing study that will be subject to 21 CFR 601.70. The study will utilize an integrated electronic health records (EHR) database with access to medical records data to further describe the safety profile of ODACTRA in marketed use in the US. 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. The primary objective of the study is to estimate the incidence of serious allergic reactions and eosinophilic esophagitis among patients exposed to ODACTRA. The study will assess the first in-office exposures to ODACTRA and subsequent exposures and outcomes (e.g., serious allergic reactions and EoE) to the extent that they are available within the EHR system.

Final protocol submission date: August 15, 2017

Study completion date: February 28, 2024

Final Report Submission date: February 28, 2025