CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209022Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 209022	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Xhance Nasal Spray Established/Proper Name: Fluticasone Propionate (OPN-375) Dosage Form: Nasal Spray Strengths: 93 mcg		
Applicant: OptiNose US, Inc.		
Date of Receipt: November 18, 2016		
PDUFA Goal Date: September 18, 2017	Action Goal Date (if different):	
RPM: Nina Ton		
Proposed Indication: Nasal polyps		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 021433 Flovent HFA (fluticasone propionate) Inhalation Aerosol	FDA's previous findings of safety
NDA 020121 Flonase (fluticasone propionate) Nasal Spray	FDA's previous findings of safety

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

A comparative bioavailability bridging study (Study 1102) comparing OPN-375 to Flonase and Flovent HFA was conducted and demonstrated that the systemic exposure to fluticasone produced by a 372-µg single dose of OPN-375, the highest proposed dose, is higher than that of a 400-µg single dose of Flonase, but lower than that observed with a 440-µg single dose of Flovent HFA. As such, the Flovent HFA RLD provided the bridge for systemic safety of the proposed product (OPN-375, tradename Xhance nasal spray). That being said, nonclinical toxicology data for the Flonase product provided support for the local nasal safety of the OPN-375 product so it is also being relied upon. This is acceptable since both products are fluticasone propionate nasal sprays and the doses administered in nonclinical toxicology studies for Flonase were large enough to cover the local exposure for the OPN-375 product. Finally, fluticasone propionate, the active moiety for Flonase, Flovent HFA, and OPN-375, is a substrate of the cytochrome P450 3A4 enzyme (CYP3A4). When administered with medications that are strong CYP3A4 inhibitors such as ritonavir, systemic exposure of fluticasone propionate increases and may be a safety concern. Because it is the same active drug at similar doses, the drug interaction studies conducted for the Flonase and Flovent HFA fluticasone products with CYP3A4 inhibitors, which are separate studies from the comparative bioavailability study referred to above, can be relied on for the OPN-375 product.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Flovent HFA (fluticasone propionate) inhalation aerosol	NDA 021433	Yes
Flonase (fluticasone propionate) nasal spray	NDA 020121	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☒ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing: Flonase

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new indication of treatment of nasal polyps in patients 18 years of age or older.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☒

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☒ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all*

of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):
NDA 208798 ArmonAir RespiClick (fluticasone propionate) Inhalation Powder
NDA 019957 Cutivate (fluticasone propionate) Ointment
NDA 019958 Cutivate (fluticasone propionate) Cream
NDA 021152 Cutivate (fluticasone propionate) Lotion
NDA 020121 Flonase (fluticasone propionate) Nasal Spray
NDA 205434 Flonase Allergy Relief (fluticasone propionate) Metered Spray
NDA 020548 Flovent (fluticasone propionate) Inhalation Aerosol
NDA 020549 Flovent (fluticasone propionate) Inhalation Powder
NDA 020833 Flovent Diskus (fluticasone propionate inhalation powder)
NDA 021433 Flovent HFA (fluticasone propionate) Inhalation Aerosol

Approved generics are also listed in the Orange Book.

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):
NDA 021433 Flovent HFA
6161724
6170717
6315173
6431168
6435372
6510969
6743413
6938796
6966467
6997349
7107986
7143908
7350676
7500444
7832351

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):
NDA 021433 Flovent HFA
5658549
5674472
6251368
6253762
6546928
6596260

NDA 020121 Flonase
4335121

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

NDA 021433 Flovent HFA
6161724
6170717
6315173
6431168
6435372
6510969
6938796
6966467
6997349
7107986
7143908
7350676
7500444
7832351
6743413

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): February 1, 2017

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☒ Patent owner(s) consent(s) to an immediate effective date of approval ☐

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PHUONG N TON
09/15/2017

PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[1] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA #	209022
PMR/PMC Set (####-#)	
Product Name:	Xhance nasal spray (fluticasone propionate)
Applicant Name:	OptiNose US, Inc.
ODE/Division:	ODEII/DPARP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Conduct a randomized, double-blind, placebo controlled, parallel group clinical study in children and adolescents 6 to 17 years of age with bilateral nasal polyps associated with nasal congestion to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of Xhance in improving nasal polyp grade and symptoms (nasal congestion/obstruction, sense of smell, rhinorrhea and facial pain or pressure).

2. PMR/PMC Schedule Milestones[2, 3]

Draft Protocol Submission:	submitted
Final Protocol Submission:	01/2018
Study/Trial Completion:	01/2022
Final Report Submission:	07/2022

[1] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[2] *Final protocol*, *study/trial completion*, and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[3] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study[4] or clinical trial[5] in the text box below.

The primary purpose of the study is to evaluate the safety and efficacy of Xhance nasal spray in pediatric patients aged 6 to 17 years of age with bilateral nasal polyps. The study is appropriate as a PMR because the safety and efficacy of Xhance nasal spray has already been demonstrated in the ≥18 year old population.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☒ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: *[Select all that apply]*

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to* approval.]

[4] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[5] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** ***[for PMCs skip to Q.5]. Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal of serious risk related to the use of the drug
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[6] and Sentinel's postmarket ARIA[7] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[6] FDA Adverse Event Reporting System (FAERS)

[7] Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: ***[Select all that apply then go to Q.4.e]***

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?**
[Select either "Yes" or "No" and provide the appropriate responses.]

☐ **Yes**, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

[Explain why a study is sufficient]

☐ **No**, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected "other," expand on the reason(s) why a study is not sufficient.]

f. ☐ **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **<u>For all PMRs and PMCs</u>: What type of study or clinical trial is needed to achieve the goal described in Q1 *<u>or</u>* Q4.a above?**
*[Select ONE OPTION only under *<u>either</u>* "Type of Study" *<u>or</u>* "Type of clinical Trial"]*

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study

TYPE OF STUDY
☐ Other (describe) _____

TYPE OF CLINICAL TRIAL
☒ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
☐ Drug interaction or bioavailability clinical trial (clinical only)
☐ Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☐ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes

☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):** ***[Select all that apply]***

- ☐ *For non-PREA pediatric studies/trials only*: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

(b) (4)

SECTION E: PMR/PMC Development Coordinator Statements[8]

1. **The PMR/PMC is clear, feasible, and appropriate[9] because:** ***[Select all that apply]***

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☒ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug's efficacy or safety.

[8] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments.*

[9] See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ **This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality**.

Insert electronic signature (usually the Deputy Director for Safety)

Appendix A
PMR/PMC Development Template (FRM-ADMIN-60)
Instructions for Use

[click here to return to the template]

Purpose:
The PMR/PMC Development template (thereafter, template) is a review tool to help the team decide that PMRs/PMCs are needed, articulate the rationale for the PMRs/PMCs, obtain initial supervisory concurrence, and to inform discussions with the applicant.

Who completes this template:
The **PMR/PMC Development Coordinator** (usually the OND division's Deputy Director for Safety) may delegate the initial draft (i.e., filling out) of the template to an **assigned reviewer**. However, the PMR/PMC Development Coordinator is responsible for ensuring the accuracy and completeness of the template and for signing off on the template.

How to complete this template:
The assigned reviewer and PMR/PMC Development Coordinator should complete the template by following the *Instructions For Use*. The PMR/PMC Development Coordinator will review each PMR/PMC to ensure it is clearly written, has an appropriate rationale, and that milestones were appropriately selected to result in timely submission of appropriate data to address the issue that prompted the PMR/PMC.

A separate template is completed for **each** individual PMR and 506B "reportable" PMC.[10] The separate templates are then combined into one document for archiving (see "How to archive the completed template").

A draft template should be completed by the date targeted to begin PMR/PMC discussions with the applicant, as documented in the Filing Letter. Once concurrence on the PMR/PMC is reached with the applicant, the draft language in the template can be finalized.

How to archive the completed template:
The OND division's Safety Regulatory Project Manager should ensure appropriate sign-off on the completed template, as determined by the division, and that the process below is followed to ensure the completed template is filed correctly.

Completed templates for all PMRs and 506B "reportable" PMCs for a specific application should be combined and filed in CDER's electronic archival system as a single document.[11] This single document should be filed as *PMR/PMC Development Template* before filing the action letter that establishes the PMR(s)/PMC(s).

For (s)NDA/(s)BLA submissions, the completed, signed template should be included in the Action Package.

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[10] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B *non-reportable* (e.g., chemistry, manufacturing, and controls (CMC)) PMCs.

[11] A single document facilitates data entry by the document room by preventing the need to upload and archive multiple templates.

Instructions:

SECTION A: Administrative Information [Click here to return to Section A of the template]

Complete each field in section A. Do not leave any fields blank.

SECTION B: PMR/PMC Information [Click here to return to Section B of the template]

1. **PMR/PMC Description:** In the textbox, enter the wording for the PMR/PMC that will go in the letter notifying the applicant of the PMR/PMC (e.g., NDA action letter) and will also display in the FDA's PMR/PMC database. The PMR/PMC description should be written clearly enough to result in the applicant's timely submission of the appropriate data to address the issue that prompted the postmarketing study or clinical trial.

   PMR/PMC descriptions are specific to the drug, indication, and issues under evaluation. Nevertheless, PMR/PMC descriptions should generally reflect the design of the clinical trial or study (e.g. randomized, double-blind, active control trial; registry based prospective cohort study), the population(s) to be studied, the exposure or intervention of interest, a comparator group (if applicable), and the study/trial goals and objectives.[12]

   Avoid limiting the PMR/PMC description to a citation of the name of a specific study or clinical trial that may be ongoing (e.g., "Complete trial ABC123, *A Randomized, Placebo-Controlled Efficacy Trial of DRUG against COMPARATOR*"). The study/trial name may be included, but in addition, the PMR/PMC description should describe the design features of the study or clinical trial. In this way, should unforeseen developments preclude completion of the named study/trial, the PMR/PMC description provides sufficient information for FDA, the applicant, and the public to determine the type of study/trial that would be considered sufficient to fulfill the PMR/PMC.

   Certain types of studies and clinical trials are commonly issued as PMRs/PMCs (e.g., drug-drug interaction trials; hepatic impairment PK trials). For these, a 'standard' PMR/PMC description may be employed ***[see Appendix B for examples]***.

2. **PMR/PMC Milestones**: List the PMR/PMC milestones in the specified format.

   Dates should be specified for all milestones. The milestone date format should be MM/YYYY; however, the milestone date format for PREA PMRs may be MM/DD/YYYY if a day is specified.

   The Final Protocol Submission, Study/Trial Completion, and Final Report Submission milestones are considered "core" PMR/PMC milestones. These are included in every PMR/PMC schedule unless they are not applicable (e.g., study/trial is ongoing; the PMR is for a medical countermeasure study/trial that will not be initiated unless there is an emergency).

[12] The PMR/PMC description may also include primary and important secondary endpoints, as relevant. Typically the PMR/PMC description should not include description of milestones or other indicators of study/trial progress (e.g., frequency of interim reports), as these are described in the PMR/PMC timetable. .

The Draft Protocol Submission milestone may be included to ensure sufficient time for FDA review and comment on the protocol before it is finalized.[13]

"Other" milestones may include interim or annual report submission or subject accrual milestones.

Typically, submission of revised labeling (to reflect results from completed studies/trials are **not** included as PMR/PMC milestones.[14]

SECTION C: PMR/PMC Rationale [Click here to return to Section C of the template]

1. Describe the review issue and the goal of the study or clinical trial.

This section should summarize the **rationale** for the study/trial. The section should not repeat the description of the PMR/PMC provided in Section B.

The summary should briefly identify the review issue (safety signal for FDAAA PMRs; efficacy or other question for non-FDAAA PMRs), cite the source of the data if it includes information external to the application, and explain the intent of the study/trial and why we think the results of the PMR/PMC will be important.

The intent of the study/trial is the explanation of what it is that FDA wants to know. Intents include, but are not limited to:

- Signal detection (e.g., detecting potential serious risks associated with the drug)
- Signal refinement (e.g., checking to determine whether an identified safety signal persists; conducting surveillance to obtain additional follow-up on a known serious risk)
- Signal evaluation (e.g., obtaining a precise estimate of the serious risk associated with a drug)

Examples of a PMR/PMC rationale:

DRUG-X is metabolized through CYPYYYY, which can be inhibited by COMMONDRUGZ. This DDI trial will evaluate whether DRUGX levels are sufficiently increased to warrant a dose reduction when used concurrently with COMMONDRUGZ, to reduce the severity and/or likelihood of serious adverse effects caused by DRUGX.

DRUG-Y is intended for chronic use in patients with CONDITIONA. During clinical development of DRUG-Y, the maximum duration of patient exposure was 6 months. This long-term efficacy trial will evaluate whether positive treatment effects are maintained when exposures exceed 6 months.

[13] "Final" implies that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial. Thus, the date for this milestone should be selected to allow for the discussion period needed to create a well-designed study or clinical trial. See FDA guidance for industry, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*.

[14] Exceptions are PREA and Accelerated Approval PMRs, since those authorities necessitate submission of revised labeling to reflect PMR results.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.

This section documents the statutory or regulatory authorities that *necessitate* that the study or clinical trial be done post-approval (e.g., confirmatory trials for accelerated approval), **or** why the issue does not preclude an approval action and can be evaluated after approval without compromising safety and efficacy considerations.

Only one option should be selected.

3. For FDAAA PMRs and 506B PMCs only

This section expands on the reasons why the FDAAA PMR or 506B PMC can be conducted post-approval and do not need to be addressed prior to approval.

This section applies only to FDAAA PMRs and 506B "reportable" PMCs because the statutory and regulatory basis is sufficient explanation for all other PMRs (i.e., PREA, accelerated approval, and animal rule PMRs).

4. For FDAAA PMRs only

This section summarizes the statutory purpose of the FDAAA PMRs, the reasons why FAERS[15] and Sentinel's ARIA[16] system are insufficient for this purpose and, as applicable, why a study is insufficient for this purpose and a clinical trial is necessary. FDA must make each of these hierarchical determinations before requiring a FDAAA PMR.

***Question 4.a*: identify the purpose of the study/clinical trial:**

As mandated by Section 505(o)(3)(A), postmarketing studies and clinical trials may be required for the three purposes listed below. Therefore to document the rationale for requiring a FDAAA PMR, you must identify one of the following:

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicates the potential for a serious risk

***Questions 4.b-d*: Explanation of whether FAERS and Sentinel's postmarket ARIA system are sufficient for the purposes described in Q1. and Q4.a.**

Studies/trials are required as FDAAA PMRs when FAERS and the ARIA system are determined to be insufficient to assess the safety issue. Responses to questions 4.b-d briefly summarize the reasons why FAERS and the ARIA system have been determined insufficient.

The explanation of why FAERS is insufficient to further characterize the serious risk(s) of concern should be informed by the FDA draft guidance, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* and by discussions with the Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology (OSE).

The explanation of why the ARIA system is insufficient to further characterize the serious risk(s) of concern should be informed by discussions with the Division of Epidemiology (DEPI) in OSE, the DEPI *ARIA Sufficiency*

[15] FDA Adverse Event Reporting System (FAERS)
[16] Active Risk Identification and Analysis (ARIA)

Memorandum, and the aforementioned FDA guidance. It is acceptable to excerpt text from the *ARIA Sufficiency Memorandum*.

***Question Q4.e*: Determination of whether a study is sufficient for the purposes described in Q1. and Q4.a.**

The explanation of why a study is (or is not) sufficient to further characterize the serious risk(s) of concern should be informed by the nature of the study (e.g., an animal study is the generally accepted standard for assessment of genotoxicity) and relevant discussions with other scientific disciplines such as Clinical Pharmacology, Pharmacology/Toxicology, and DEPI.

Examples of situations when an *observational* study may not be sufficient, and a clinical trial required, in include (but are not limited to):

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of outcome(s)/endpoint(s)

***Question Q4.f*: Conclusion that only a clinical trial is sufficient for the purposes described in Q1. and Q4.a.**

Under FDAAA, when FAERS, the ARIA system, and a study are considered insufficient, then a clinical trial is necessary for the specified purposes.

5. For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal?

This section should be completed for all PMRs and PMCs.

Select the best summary description of the type of postmarketing study or clinical trial. Select only **ONE** option under either "type of study" or "type of clinical trial." Do not choose a option under both categories.

SECTION D: PMR/PMC Additional information [Click here to return to Section D of the template]

This section provides additional information about the PMRs and PMCs.

1. Does this PMR/PMC apply to other drugs (e.g. drugs in a therapeutic class)?

Select "yes" if the PMR/PMC will apply to other drugs in the same therapeutic class or different formulations of the same drug.

2. This study or clinical trial focuses on the following special population or circumstances:

Select the appropriate box(es) if the study or trial focuses on a special population. If not, select "not applicable."

3. (Complete if applicable) Additional comments about the PMR/PMC.

Complete this text box only if there are additional comments to add about this PMR or PMC (e.g., points or concerns not previously described; explanation for inclusion of additional milestones besides the 3 "core" milestones).

Note: Additional milestones also must be tracked by the division (see MAPP 6010.2, *Responsibilities for Tracking and Communicating the Status of Postmarketing Requirements and Commitments*).

If nothing additional to add, leave text box blank.

SECTION E: PMR/PMC Development Coordinator Statements [Click here to return to Section E of the template]

This section is completed only by the the PMR/PMC Development Coordinator (usually the OND division's Deputy Director for Safety) who will sign off on the completed Development Template.

1. **The PMR/PMC is clear, feasible, and appropriate because (select all that apply):**

   Select the considerations FDA made to determine that the study or clinical trial is feasible to conduct, appropriately described, and informed by discussions with the applicant.

2. **The following ethical considerations were made with regard to randomized, controlled, clinical trials:**

   This section is only completed if the PMR/PMC is for a randomized, controlled, clinical trial, including a clinical pharmacology trial.

   It is necessary to provide this information in order to demonstrate that the relevant ethical considerations have been made regarding the trial, as recommended to FDA in the Institute of Medicine's *Ethical and Scientific Issues in Studying the Safety of Approved Drugs*.

3. **This PMR/PMC has been reviewed for clarity and consistency… reliability of drug quality**.

   This attestation is to document that the necessary considerations have been made regarding the need for and appropriateness of the postmarketing study or clinical trial.

APPENDIX B

Examples of Standard Descriptions for Certain Clinical Pharmacology PMRs and PMCs

1. Examples of standard language for Clinical Pharmacology PMRs

- Renal Impairment

  Conduct a clinical pharmacokinetic trial to determine an appropriate dose of DRUG to minimize toxicity in patients with renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

- Hepatic Impairment

  Conduct a clinical pharmacokinetic trial to determine an appropriate dose of DRUG to minimize toxicity in patients with hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

- Drug-Drug Interactions-victim drug (CYP inhibitors, UGT or transporter)

  Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of CYP (or other enzyme/transporter) #X# inhibitor on the single dose pharmacokinetics of DRUG to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

- Drug-Drug Interactions-perpetrator drug as inhibitors of CYP#X#

  Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of DRUG on the single dose pharmacokinetics of XYZ drug (a sensitive CYP#X# substrate) to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

2. Examples of standard language for Clinical Pharmacology PMCs

PMCs to assess for potential decreased drug exposure, with potential loss of efficacy**.**

- Drug-Drug Interactions (gastric acid reducing agents)

  Conduct a clinical pharmacokinetic trial to evaluate if gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists, and antacids) alter the bioavailability of DRUG and to determine appropriate dosing recommendations for DRUG with regard to use of concomitant gastric acid reducing agents.

- Drug-Drug Interactions-Induction

  Conduct a clinical pharmacokinetic trial with repeat doses of a CYP#X# inducer on the single dose pharmacokinetics of DRUG to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

- Anti-Drug Antibody Responses

  Conduct an assessment of binding and neutralizing anti-drug antibody (ADA) responses with a validated assay (requested in PMC X) capable of sensitively detecting ADA responses in the presence of DRUG levels that are expected to be present in the serum at the time of patient sampling. The ADA response will be evaluated in at least ### DRUG-treated patients. The final report will include information on the level of DRUG in each patient's test sample at each sampling point.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SALLY M SEYMOUR
09/10/2017

HUMAN FACTORS RESULTS AND LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	August 9, 2017
Requesting Office or Division:	Division of Pulmonary, Allergy, Rheumatology Products
Application Type and Number:	NDA 209022
Product Name and Strength:	Xhance (Fluticasone Propionate) Nasal Spray 93 mcg per spray
Product Type:	Single-Ingredient combination product
Rx or OTC:	Rx
Applicant/Sponsor Name:	OptiNose US, Inc.
Submission Date:	November 18, 2016 and June 19, 2017
OSE RCM #:	2016-2836 and 2017-140
DMEPA Primary Reviewer:	Lissa C. Owens, PharmD
DMEPA Team Leader:	Sarah K. Vee, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS

1 REASON FOR REVIEW

This review responds to a request from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to review the Human Factors (HF) validation study report, proposed container label, carton labeling, instructions for use (IFU), and Prescribing Information (PI) submitted on November 18, 2016 as a 505(b)(2) submission under NDA 209022. As part of the approval process for Xhance, we reviewed the HF validation study report and proposed labeling for any vulnerability from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 HUMAN FACTORS VALIDATION STUDY

A total of 15 untrained participants clinically diagnosed with chronic sinusitis and/or nasal polyps participated in the Human Factors validation study (see Appendix C). We note that DMEPA did not previously review the HF protocol. However, we find the protocol that was submitted as part of the NDA acceptable (See Appendix C). The participants performed two dose administrations. After the first dose administration, the participants were administered distractor tasks (Near Vision Acuity Test, the Health Assessment Questionnaire, Pinch Grip Test, and the Ishihara Color Blindness Test) to simulate a cognitive decay period before the second dose administration. Each dose administration contained 14 tasks, which were categorized as either critical or essential (Appendix C). We discuss the use errors that occurred during the validation testing below.

Task 1: Shake product well

One participant did not shake the product during the second dose administration although this participant had correctly performed this task during the first dose administration. The

participant stated that they did not shake the product because they had done so fairly recently. They further stated that if they had been in a real situation they would have shaken the product again and understood that it should be shaken prior to each dose. Shaking the product well is not considered a critical task as the patient will still receive a dose and therefore is not clinically significant. We do not have any recommendations at this time.

Task 3: Prime the product

Two participants did not prime the product during the first dose administration. The first participant stated that they did not feel anything but did not want to get too much medication and therefore would not have tried again but would have called the pharmacist. Priming the product is not considered a critical task as the patient would initially receive a partial dose and after use of the product for seven doses, they would receive the full dose. Although, the initial dose may be less than the full dose, this is not clinically significant as this is a maintenance medication and not intended as a rescue device. There were no modifications proposed to the user interface or to the IFU and we agree that no modifications are necessary at this time.

Task 4 & 9a: Grip product in such a way that it does not hinder use of device

One participant placed his fingers over the mouthpiece while priming and shaking the device during both dose administrations. The participant was able to deliver the correct dose. The participant stated that he did not realize he was holding the device incorrectly and that he was nervous and rushing. In this error the participants grip was over the mouthpiece only and therefore the dose is still delivered to the patient. The participant still received the dose and therefore this error would not be clinically significant. There were no modifications proposed to the user interface or to the IFU. However, we believe that changes to the IFU may help to increase the prominence of not placing fingers over or above the mouthpiece. We make recommendations in Section 4.2.

3.2 LABEL AND LABELING

DMEPA also reviewed the proposed container labels, carton labeling, and the PI to determine whether there are any significant concerns in terms of safety related to preventable medication errors. We note that the proposed proprietary name on the carton labeling may be improved to increase readability.

4 CONCLUSION & RECOMMENDATIONS

We find the results of the Human Factors Validation Study acceptable. In addition, we find the container labels acceptable. However, we have recommendations for the PI, instructions for use, and carton labeling in sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Consider replacing the [redacted] (b) (4) with their intended meanings to prevent misinterpretation and confusion.

4.2 RECOMMENDATIONS FOR OPTINOSE

We recommend the following be implemented prior to approval of this NDA:

A. Carton Labeling

1. In order to increase the readability of the proprietary name, we recommend not using graphic font for any part of the proprietary name. We recommend that the entire proprietary name be presented in the same font.

B. Instructions For Use

1. Your human factors study results indicated that one participant placed his fingers over the mouthpiece while priming and shaking the device during both dose administrations. To further address this, we ask that you add the statement 'Do Not place your finger above or over the Flexible Mouthpiece.' to the beginning of the IFU after the warning 'Do Not block your second nostril while blowing.' to increase the prominence of this warning.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xhance that OptiNose submitted on November 18, 2016.

Table 2. Relevant Product Information for Xhance	
Initial Approval Date	N/A
Active Ingredient	Fluticasone Propionate
Indication	treatment of nasa (b) (4) in patients 18 years of age or older
Route of Administration	Intranasal
Dosage Form	Nasal Spray
Strength	93 mcg per spray
Dose and Frequency	1 to 2 sprays twice a day
How Supplied	1 unit (device prefilled with drug) per carton
Storage	Store at room temperature between (b) (4) -25°C ((b) (4) -77°F). (b) (4)

APPENDIX C. HUMAN FACTORS STUDY

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APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Xhance labels and labeling submitted by OptiNose US, Inc. on November 18, 2016 and June 19, 2017.

- Container label
- Carton labeling
- Professional Sample Carton Labeling
- Professional Sample Container Label
- Instructions for Use (Image not shown)
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LISSA C OWENS
08/09/2017

SARAH K VEE
08/10/2017

QUYNHNHU T NGUYEN
08/14/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 9, 2017
To:	Badrul Chowdhury, MD, PhD Director **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Taylor Burnett, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	XHANCE (fluticasone propionate)
Dosage Form and Route:	Nasal Spray, 93 mcg
Application Type/Number:	NDA 209022
Applicant:	OptiNose US, Inc.

1 INTRODUCTION

On November 18, 2016, OptiNose US, Inc. submitted for the Agency's review an original New Drug Application (NDA) 209022 for XHANCE (fluticasone propionate) Nasal Spray, 93 mcg. The proposed indication for XHANCE (fluticasone propionate) Nasal Spray, 93 mcg is for the treatment of nasal polyps in patients 18 years of age or older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on January 3, 2017 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for XHANCE (fluticasone propionate) Nasal Spray, 93 mcg.

2 MATERIAL REVIEWED

- Draft XHANCE (fluticasone propionate) Nasal Spray, 93 mcg PPI and IFU received on November 18, 2016 and received by DMPP and OPDP on July 26, 2017.
- Draft XHANCE (fluticasone propionate) Nasal Spray, 93 mcg Prescribing Information (PI) received on November 18, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 26, 2017.
- Approved DYMISTA (azelastine hydrochloride and fluticasone propionate) nasal spray, for oral use, comparator labeling dated February 20, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI and IFU document using the Arial font, size 10 and 11 respectively.

In our collaborative review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

DMPP Patient Labeling Comments for NDA 209022 XHANCE (fluticasone propionate) Nasal Spray, 93 mcg

General patient labeling comments:

- The embedded formatting in the XHANCE (fluticasone propionate) Nasal Spray, 93 mcg IFU prevents DMPP from providing a marked version of the document. We have provided these patient labeling comments as a separate WORD document to ensure the IFU is consistent with current patient labeling.
- Patient labeling materials should meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).
- To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.
- Patient labeling materials should be in fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We recommend Arial font, size 11.
- Patient labeling materials should utilize simple wording and clear concepts where possible and should be consistent with the Prescribing Information.
- Do not use underlining, italics, all capital letters or text boxes in patient labeling as it is difficult to read for patients with low or impaired vision. Use bolded text instead to highlight important information.
- Use bold text for headers and to highlight important text only. Overuse of bolding minimizes the importance of certain important information for the patient.
- Do not use a font color for text other than black. The use of other font colors may make the text difficult for people with low vision and color blindness to read.

Comments specifically for the Instructions for Use (IFU):

- The DMPP review of the XHANCE (fluticasone propionate) Nasal Spray, 93 mcg IFU has provided revisions for more patient friendly language and clarification of steps to increase patient comprehension and readability. As part of these efforts, we have also implemented several formatting changes. DMPP extracted the content of the IFU and included this information below to provide a marked version with patient labeling comments.

INSTRUCTIONS FOR USE
XHANCE (phonetic spelling)
(fluticasone propionate)
Nasal Spray, 93 mcg

Read (b) (4) Instructions for Use before you start using XHANCE and each time you get a refill.

There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. If you have any questions about XHANCE, ask your healthcare provider or pharmacist.

Parts of [redacted] XHANCE [redacted]
[Figure A]

Important information about XHANCE

- **XHANCE is for use in your nose only. Do not spray in your eyes [redacted] mouth.**
- [redacted] XHANCE [redacted] delivers your dose of medicine into your nose when you press the Bottle while blowing into the Flexible Mouthpiece (**See Figure B**).
- Do not share XHANCE with other people.
- **Shake XHANCE [redacted] before each use.**

[Figure B]

[redacted]

[redacted] **XHANCE** [redacted]

Step 1: Remove the Cap (**See Figure C**).

Step 2: Shake [redacted] XHANCE [redacted]

Step 3: Press the Bottle 7 times or until you see a fine mist (**See Figure D**). Keep the Tapered Tip of [redacted] XHANCE [redacted] pointed away from your face while priming. When you see a fine mist of medicine, XHANCE is ready to use.

Important: If you have not used XHANCE for 7 or more days, re-prime by spraying 2 times away from your face.

Steps for using [redacted] XHANCE [redacted] after priming

Step 1: Remove Cap.

Step 2: Shake [redacted] XHANCE [redacted] (**See Figure E**).

Step 3: Hold [redacted] **by placing your fingers on the Indented Grip below the Flexible Mouthpiece.** You can use 1 hand (**See Figure F**), or 2 hands (**See Figure G**) to hold [redacted]

Do not place your fingers above or over the Flexible Mouthpiece.

Step 4: Gently insert the Nosepiece into the nostril. While still holding [redacted] on the Indented Grip below the Flexible Mouthpiece, insert the Nosepiece as far back into 1

nostril as comfortable (**See Figure H**). This helps to keep a tight seal between the Nosepiece and your nostril.

[redacted] keep a tight seal between the Nosepiece and your nostril.

Step 5: Insert the Flexible Mouthpiece in your mouth, while keeping the Nosepiece in your nostril (**See Figure I**). Make sure that the Flexible Mouthpiece is secure in the mouth and the Nosepiece [redacted] in the nostril during use [redacted]

Note: You can bend the Flexible Mouthpiece up and down to get it into your mouth while keeping the Nosepiece deep [redacted] your nostril.

Step 6: Aim the device upward. This will help the medicine go deep into your nostril (**See Figure J**).

Note: You can use a mirror to help you aim the device upward.

Step 7: Blow hard into the Flexible Mouthpiece like you are blowing up a balloon (**See Figure K**).

Do not try to breathe in through your nose or sniff while blowing into the Flexible Mouthpiece.

Do not close or block your other nostril. This could prevent the air you blow into the Flexible Mouthpiece from leaving out through the other nostril.

Step 8: While still blowing hard into the Flexible Mouthpiece, use your [redacted] to press the Bottle [redacted] to deliver [redacted] medicine into your nostril (**See Figure L**).

Step 9: Repeat Steps 2 to 8 in the "Steps for using [redacted] XHANCE [redacted] after priming" to deliver the medicine into your other nostril.

Cleaning [redacted] XHANCE [redacted]

- You do not need to clean [redacted] XHANCE [redacted] If you prefer to clean the device, remove the Cap and use a clean, dry, lint-free cloth to wipe [redacted] after each use.
- Replace the Cap and store [redacted] in a clean, dry place. [redacted]
- The XHANCE Bottle is made of glass and can break if dropped or hit too hard. If you accidentally drop [redacted], check it for damage. [redacted]

How should I store XHANCE?

- Store [redacted] at room temperature between [redacted]
- Protect XHANCE from light.

- Throw away XHANCE after using 120 sprays after initial priming. Even though the Bottle may not be completely empty, you may not get the correct dose of medicine if you continue to use it.

Keep XHANCE and all medicines out of the reach of children.

(b) (4) Instructions for Use (b) (4) been approved by the U.S. Food and Drug Administration.

[Manufacturing and trademark information]

Issued: Month Year

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/s/

NYEDRA W BOOKER
08/09/2017

TAYLOR B BURNETT
08/09/2017

MARCIA B WILLIAMS
08/10/2017

LASHAWN M GRIFFITHS
08/10/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 9, 2017

To: Nina Ton, Pharm.D.
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Taylor Burnett, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm.D., RAC
Team Leader
OPDP

Subject: OPDP Labeling Comments for XHANCE (fluticasone propionate) Nasal Spray, 93 mcg (Xhance)

NDA: 209022

In response to DPARP's consult request dated January 3, 2017, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for Xhance.

OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DPARP on July 26, 2017, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI and IFU will be sent under separate cover.

OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on June 19, 2017, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Taylor Burnett at (240) 402-1349 or Taylor.Burnett@fda.hhs.gov.

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/s/

TAYLOR B BURNETT
08/09/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Food and Drug Administration
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Division of Pediatric and Maternal Health Review

Date: 7/21/2017 **Date consulted:** 1/12/2017

From: Catherine Roca, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D., OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

Drug: XHANCE (fluticasone propionate nasal spray)

NDA: 209022

Applicant: OptiNose US, Inc.

Subject: Pregnancy and Lactation Labeling

Indication: Nasal (b) (4) in patients ages 18 or older

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 209022
- DPMH review of FLOVENT (fluticasone), NDA 20833/S-31 and NDA 21433/S-031, Carol Kasten, M.D., Medical Officer, July 21, 2016. DARRTS Reference ID 3962097

Consult Question: Please review the labeling content and format for the requirements of Pregnancy and Lactation Labeling Rule (PLLR), specifically the Human Data under Section 8.1

where the Sponsor has described clinical experience in pregnant women that received intranasal or inhaled fluticasone propionate or glucocorticoids from the published literature.

INTRODUCTION

The Division of Pulmonary, Allergy and Rheumatology Products (DPARP) consulted the Division of Pediatric and Maternal Health (DPMH) on January 12, 2017 requesting input regarding the applicant's labeling proposal, more specifically the proposed PLLR language (Sections 8.1/8.2).

REGULATORY HISTORY

On November 19, 2016 the applicant, OptiNose US, Inc.submitted an original 505(b)(2) NDA 209022 based on the reference listed drugs FLONASE (fluticasone propionate) Nasal Spray (NDA 020121) and FLOVENT HFA (fluticasone propionate) inhalation aerosol (NDA 021433). The NDA 209022 is for an exhalation drug delivery system that delivers fluticasone propionate intra-nasally for the treatment of nasal (b) (4) in patients ages 18 and older.

BACKGROUND

Drug Characteristics[1]

Fluticasone propionate is a corticosteroid. It has an anti-inflammatory effect on multiple inflammatory cell types as well as chemical mediators of inflammation, such as cytokines. The recommended total daily dose for the indication of nasal (b) (4) ranges between 372 and 744 mcg. This differs from the dose range recommended for inhaled fluticasone propionate (FLOVENT HFA) for asthma. The highest recommended daily dosage for asthma ranges from 880 to 1750 mcg/day. Fluticasone characteristics include:

- molecular weight of 500.57 Daltons
- approximately 99% protein bound
- terminal half-life of 7.8 hours
- oral bioavailability <1%

Serious adverse effects from Phase 3 clinical trials include local effects such as nasal ulceration, epistaxis, nasal perforation and infection. There are no warnings related to embryofetal toxicity.

Nasal (b) (4) and Pregnancy

Chronic rhinosinusitis (CRS) is a clinical syndrome characterized by mucosal inflammation of the nose and paranasal sinuses. It is generally divided into two broad categories – with and without nasal polyposis. Chronic rhinosinusitis with nasal polyposis (CRSwNP) is often associated with asthma, aspirin sensitivity, and idiopathic bronchiectasis.[2] CRS affects 13% of adults in the United States.[3] Untreated rhinitis during pregnancy may exacerbate existing asthma, and therefore consideration of treatment may be important to avoid adverse pregnancy outcomes.[4] Further, nasal obstruction in pregnancy can cause snoring, which has been

[1] Flovent labeling, Drugs@FDA.gov, accessed 5/24/2017.
[2] Bachert C, et al. Current and future treatment options for adult chronic rhinosinusitis: Focus on nasal polyposis. J All Clin Immunol. 2015. 136(6):1431-1440.
[3] Summary Health Statistics for US Adults: National Health Interview Survey, 2008. CDC Center for National Health Statistics 2009. 10:(242) pg. 5.
[4] Schatz M and Zeiger RS. Asthma and allergy in pregnancy. Clin Perinatol. 1997/ 24(2): 407-32.

associated with pregnancy-induced hypertension and intrauterine growth retardation (IUGR).[5] Therapies considered to be low-risk for CRS during pregnancy include intranasal sodium cromoglycate, beclomethasone, budesonide and first generation antihistamines. Some authors suggest that intranasal corticosteroids should be considered first line treatment in allergic rhinosinusitis, due to their efficacy and lack of association with congenital anomalies.[6,7,8]

Current State of the Labeling[9,10]

The labeling for the reference drug, FLONASE is in PLR, but not PLLR format. FLOVENT HFA was recently updated (4/2017) and is in PLLR format. FLONASE is labeled Category C for pregnancy. There are no boxed warnings. In the updated FLOVENT HFA labeling, no human data are presented in the Pregnancy or Lactation sections. There are no contraindications for pregnancy or lactation, and no listed drug interactions with hormonal contraceptives. Section 8.3 is not included in the current FLOVENT HFA labeling.

Pregnancy and Lactation Labeling

On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[11] also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule[12] format to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW

PREGNANCY

Nonclinical Experience

In embryofetal development studies with pregnant rats and mice dosed by the subcutaneous route throughout the period of organogenesis, fluticasone propionate was teratogenic in both species. Omphalocele, decreased body weight, and skeletal variations were observed in rat fetuses, in the presence of maternal toxicity, as a dose approximately 1.31 times the maximum recommended human daily inhaled dose (MRHDID) (on a mg/m^2 basis with a maternal subcutaneous dose of 30 mcg/kg/day). Cleft palate and fetal skeletal variations were observed in mouse fetuses at a

[5] Franklin KA, et al. Snoring, pregnancy-induced hypertension, and growth retardation of the fetus. Chest. 2000. 117:137-141.

[6] Lai D, et al. Management of rhinosinusitis during pregnancy: systematic review and expert panel recommendations. Rhinology. 2016. 54:99-104.

[7] Mazzotta P, et al. Treating allergic rhinitis during pregnancy. Drug Safety. 1999. 20(4):361-375.

[8] Gilbert C, et al. Fetal safety of drugs used in the treatment of allergic rhinitis: a critical review. Drug Safety. 2005. 28(8): 707-719.

[9] FLONASE approved package insert. Accessed at Drugs@FDA.gov May 21, 2017.

[10] FLOVENT HFA approved package insert. Accessed at Drugs@FDA.gov May 24, 2017.

[11] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

[12] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

dose approximately 0.29 times the MRHDID (on a mg/m^2 basis with a maternal subcutaneous dose of 15 mcg/kg/day).

In embryofetal development studies with pregnant rats and mice dosed by the inhalation route throughout organogenesis, fluticasone propionate produced decreased fetal body weights and skeletal variations, in the presence of maternal toxicity, at a dose approximately 0.34 times the maximum recommended human daily inhaled dose (MRHDID). No congenital anomalies were detected. The reader is referred to the full Pharmacology/Toxicology review by Brett Jones, Ph.D. and Tim Robinson, Ph.D.

Review of Literature

The applicant performed a search of the literature using PubMed and the following search terms, "fluticasone and pregnancy" and "fluticasone and safety" from October 9, 2015 to December 31, 2016. The search yielded one article.

> Battista, et al.[13] enrolled 17 pregnant women with asthma who were taking inhaled fluticasone alone or in combination with salmeterol throughout pregnancy and compared them to 24 pregnant women without chronic medical conditions or corticosteroid use. Cord and maternal blood samples were collected. Concentrations of fluticasone propionate ranged from 0.423 to 4.510 pg/mL in cord blood and 1.247 to 46.444 pg/mL in maternal blood. Results demonstrated placental passage of inhaled fluticasone propionate. ACTH was also suppressed by approximately 33% in mothers taking fluticasone propionate (p=0.04) compared to control mothers.

DPMH Review of Literature:

DPMH conducted a review of the literature using PUBMED, Embase, and Reprotox using the search terms, "fluticasone" and the following terms, "pregnancy," "pregnant women," "pregnancy and birth defects," "pregnancy and fetal malformations," "pregnancy and still birth," "spontaneous abortion," and "miscarriage."

Fluticasone is referenced in TERIS[14] which reports it is unknown if fluticasone crosses the placenta. It also states, "Therapeutic doses of fluticasone during pregnancy are unlikely to pose a substantial teratogenic risk, but the data are insufficient to state that there is no risk."

Regarding inhaled and nasal preparations of fluticasone Shepard's Catalog of Teratogenic Agents states,

> "In a prescription event monitoring study performed in general practices in the United Kingdom, the frequency of congenital anomalies was not significantly increased among the children of 3,311 women who were treated during the first trimester of pregnancy with inhaled fluticasone either alone or in combination with salmeterol for asthma when compared to the children of women who were treated for asthma with other inhaled

[13] Battista M-C, et al. Maternal inhaled fluticasone propionate intake during pregnancy is detected in neonatal cord blood. Bioanaly. 2016. 8(14):1441-1450.
[14] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 5/30/2017.

glucocorticoids during pregnancy.[15] Similarly, no association with maternal fluticasone treatment one month before conception through the first trimester of pregnancy was observed among 1,165 male infants with hypospadias, 2,662 infants with cleft lip with or without cleft palate, or 1,410 infants with cleft palate alone in National Birth Defects Prevention Study cases ascertained between 1997-2009[16,17] and 2003-2009.[18] The frequency of congenital anomalies was not significantly increased among 1,231 children born to women who had received inhaled glucocorticoids during pregnancy in the Danish National Birth Cohort (odds ratio=1.08, 95% confidence interval 0.85-1.37).[19] Fluticasone was used by 18% of the women in this cohort. In a record linkage study, no association was found with any congenital malformation among the infants of 587 mothers who were treated for asthma with fluticasone early in pregnancy.[20,21] Meta-analysis of four observational cohort studies of infants born to asthmatic women treated with various inhaled corticosteroids during pregnancy in comparison with infants of asthmatic women who did not receive treatment showed no difference in the risk of major malformations, low birth weight, or preterm birth.[22]

In a clinical series of 15 infants whose mothers had been treated during the first trimester of pregnancy with fluticasone in combination with salmeterol, one infant died with nonketotic hyperglycemia and another had a small ventricular septal defect that closed without intervention before one month of age.[23] No congenital anomalies were reported among 10 infants whose mothers had taken fluticasone during pregnancy and called a teratogen information service.[24] All but one of the women who called the service used fluticasone during the first trimester of pregnancy.

No adverse effects were observed among the infants of 26 women who were recruited for treatment of rhinitis with fluticasone during the third trimester of pregnancy in a randomized, double-blind study. No significant reduction in birth weight, length, or head

[15] Charlton et al. Safety of fluticasone propionate prescribed for asthma during pregnancy: a UK population-based cohort study. J Allergy Clin Immunol Pract. 2015. 3(5):772-779,
[16] Carmichael SL, et al. Maternal corticosteroid use and orofacial clefts. Am J Obstet Gynecol. 2007. 197(6):585.e-585.e7.
[17] Carmichael SL, et al. Maternal corticosteroid use and hypospadias. J Pediatr. 2009. 155(1):39-44.
[18] Skuladottir H, et al. Corticosteroid use and the risk of orofacial clefts. Birth Defects Res A Clin Mol Teratol. 2014. 100(6):499-506.
[19] Tegethoff M, et al. Inhaled glucocorticoids during pregnancy and offspring pediatric diseases: a national cohort study. Am J Resprir Crit Care Med. 2012. 185(5):557-563.
[20] Kallen B and Otterblad Olausson P. Use of anti-asthmatic drugs during pregnancy. 1. Maternal charachteristics, pregnancy and delivery complications. Eur J Clin Pharmacol. 2007a. 63(4):363-373.
[21] Kallen B and Otterblad Olausson P. Use of anti-asthmatic drugs during pregnancy. 3. Congenital malformations in the infants. Eur J Clin Pharmacol. 2007b. 63(4):363-373.
[22] Rahimi R, et al. Meta-analysis finds use of inhaled corticosteroids during pregnancy safe: a systematic meta-analysis review. Hum Exp Toxicol. 2006. Hum Exp Toxicol. 25(8):447-452.
[23] Perrio MJ et al. A modified prescription-event monitoring study to assess the introduction of Flixotide Evohaler into general practice in England: an example of pharmacovigilance planning and risk monitoring. Pharmacoepidemiol Drug Saf. 2007. 16(9):969-978.
[24] Choi JS, et al. Pregnancy outcomes in women using inhaled fluticasone during pregnancy: a case series. Allergol Immunopathol. (Madr). 2007. 35(6):239-242.

circumference was found among 31 infants whose mothers used inhaled fluticasone during pregnancy for the treatment of asthma in a prospective cohort study."[25]

A search of the literature using PubMed and Embase located the one study on nasal fluticasone and pregnancy; the same study referenced by Shepard's.[25] A detailed review of the effects of inhaled corticosteroids can be found in the DPMH consult review of FLOVENT HFA, Carol Kasten, MD, DARRTS Reference ID 3962097. In summary, neither nasal nor inhaled corticosteroids were associated with an increased risk of congenital malformations or adverse pregnancy outcomes.

Review of Pharmacovigilance Database

The applicant performed a search for the FDA FAERS[26] database for adverse drug events relating to fluticasone propionate formulations either alone or in combination with other drug products, such as long-acting beta agonists from Jan. 1, 2014-December 31, 2016, using the search terms "fluticasone propionate," "Flonase," "Flovent," "Advair," "Asmatil," "Atemur," "Axotide," "Bethal." "Flixotide," "Flixonase," "Flunase." "Flutide," "Flutivate," "Inalacor," "Rinosome," "Seretide," "Trialona," "Ubizol," "Veramyst," and "Zoflut." The applicant found 33,250 cases of safety reports, which included some cases that had more than one safety report. Of these, seven individual reports of congenital anomaly were reported. No details were provided on the specific nature of the anomalies.

Summary

While the data regarding the use of nasal preparations of fluticasone propionate in pregnancy are limited, data from studies of inhaled fluticasone propionate do not indicate an increased risk of adverse pregnancy outcomes.

LACTATION

Nonclinical Experience

A Pharmacology Toxicology review for FLOVENT HFA (NDA 021433) by Lawrence Sancilio, Ph.D. dated December 20, 2002[27] stated that radioactivity was found in the breast milk of lactating rats subcutaneously administered tritiated fluticasone propionate.

Applicant's Review of Literature

The applicant performed a search of PubMed using the terms, "fluticasone and lactation," and "fluticasone and breast." No articles were found in the search.

DPMH Review of the Literature

DPMH conducted a search of *Medications in Mother's Milk,*[28] the Drugs and Lactation Database (LactMed),[29] Micromedex,[14] and of the published literature in PubMed and Embase using the search terms "fluticasone," and "lactation," and "breastfeeding."

[25] Ellegard, EK, et al. Fluticasone propionate aqueous nasal spray in pregnancy rhinitis. Clin Otolaryngol. 2001. 26:394-400.

[26] Summary of Adverse Event Cases reported into the US FDA Adverse Event Reporting System (FAERS) where fluticasone was reported with an administration route of (intranasal, nasal, oropharingeal, respiratory (inhalation), unknown or blank) and an initial FDA receipt date on or after 1 July 2015.

[27] See Drugs@FDA.gov.

[28] Hale TW and Rowe HE. (2017) Medications and Mother's Milk. Springer Publishing Company, LLC. New York, NY.

Fluticasone is referenced in Medications and Mother's milk[30] and is rated, "L3 – no data, probably compatible." Thomas Hale, a lactation expert states, "When instilled intranasally, the absolute bioavailability is less than 2%, so virtually none of the dose is absorbed systemically. Oral absorption following inhaled fluticasone is approximately 30%, although almost instant first pass absorption virtually eliminated plasma levels of fluticasone.[31] Plasma levels are not detectable when using suggested doses. Although fluticasone is secreted into milk of rodents, the dose used was many times higher than found under normal conditions. With the above limited oral and systemic bioavailability and rapid first pass uptake by the liver, it is not likely that milk levels will be clinically relevant, even with rather high doses."

Fluticasone is also referenced in *Drugs in Pregnancy and Lactation*[32], which rates fluticasone as "probably compatible with breastfeeding."

LactMed states, "Although not measured, the amounts of inhaled corticosteroids absorbed into the maternal bloodstream and excreted into breastmilk are probably too small to affect a breastfed infant. Reviewers and an expert panel consider inhaled corticosteroids acceptable to use during breastfeeding.[33,34,35]

Review of Pharmacovigilance Database

No pharmacovigilance data on fluticasone and breastfeeding were provided.

Summary

The amount of inhaled fluticasone that is transferred into human milk has not been measured. A nonclinical study with tritiated fluticasone propionate was reported to demonstrate transfer of the drug into the milk of lactating rats. There are species differences in the transfer of drugs into breast milk. Rat data on drug transfer into milk are not reliable indicators of the levels of fluticasone that may be present in a breastfeeding mother's milk. Fluticasone concentrations in the plasma are low and the low bioavailability of fluticasone is less than 1%, which reduces the exposure to fluticasone in a breastfed infant.

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[29] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

[30] Hale TW and Rowe HE. (2017) Medications and Mother's Milk. Springer Publishing Company, LLC. New York, NY. pp. 397-8.

[31] Harding SM. The human pharmacology of fluticasone propionate. Respir Med 1990. 84 Suppl A:25-29.

[32] Briggs GG and Freeman RK. Drugs in pregnancy and lactation. Wolter Kluwer. 2015. Philadelphia, PA. pp. 576-577

[33] Greenberger, PA and Patterson, R. The management of asthma during pregnancy and lactation. Clin Rev Allergy. 1987. 5:317-24.

[34] Ellsworth A. Pharmacotherapy of asthma while breastfeeding. J Hum Lact. 1994. 10:39-41.

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FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

The nonclinical studies did not demonstrate an adverse effect of fluticasone on animal fertility.

Applicant's Review of Literature

The applicant performed a PubMed search using the terms "reproduction" or "contraception" and "fluticasone," which did not yield any references.

DPMH Review of Literature

DPMH performed a literature review of Embase and PubMed using the search terms, "fluticasone fertility," "fluticasone and sperm," "fluticasone and reproductive endocrinology," "fluticasone and hormonal contraceptives," and "fluticasone and ovulation."

No studies on fluticasone and fertility or hormonal contraceptive agents were found in the searches of the published literature.

Review of Pharmacovigilance Database

No pharmacovigilance data on fluticasone and fertility issues were provided.

Summary

There are no reports in the nonclinical data or the published literature of adverse effects on reproductive potential from nasal or inhaled fluticasone propionate. Subsection 8.3 may be omitted from labeling.

CONCLUSIONS

- **Pregnancy, Section 8.1**
  - The "Pregnancy" section of labeling was formatted in the PLLR format to include: "Risk Summary," and "Data" sections.
- **Lactation, Section 8.2**
  - The "Lactation" section of labeling was formatted in the PLLR format to include: the "Risk Summary" section.
- **Patient Counseling Information, Section 17**
  The "Patient Counseling Information" section of labeling was updated to correspond with changes made to sections 8.1 and 8.2 of labeling.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1, 8.2, and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling. (See Appendix A for the applicant's proposed pregnancy and lactation labeling.)

DPMH Proposed Pregnancy and Lactation Labeling

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published literature on the use of inhaled or intranasal fluticasone propionate in pregnant women have not reported a clear association with adverse developmental outcomes. Inhaled fluticasone crosses the placenta *[see Data and Clinical Pharmacology (12.x)]*. In animals, teratogenicity characteristic of corticosteroids, decreased fetal body weight, and/or skeletal variations in rats, mice, and rabbits were observed with subcutaneously administered maternal toxic doses of fluticasone propionate less than the maximum recommended human daily inhaled dose (MRHDID) on a mg/m^2 basis. However, fluticasone propionate administered via inhalation to rats decreased fetal body weight, but did not induce teratogenicity at a maternal toxic dose less than the MRHDID *(see Data)*. Experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

Based on published literature, inhaled fluticasone propionate has been shown to cross the placenta *[see Clinical Pharmacology (12.x)]*. The clinical significance for intranasal fluticasone is unknown.

Animal Data

In embryofetal development studies with pregnant rats and mice dosed by the subcutaneous route throughout the period of organogenesis, fluticasone propionate was teratogenic in both species. Omphalocele, decreased body weight, and skeletal variations were observed in rat fetuses, in the presence of maternal toxicity, at a dose approximately 0.5 times the MRHDID (on a mg/m^2 basis with a maternal subcutaneous dose of 100 mcg/kg/day). The rat no observed adverse effect level (NOAEL) was observed at approximately 0.17 times the MRHDID (MRHDID (on a mg/m^2 basis with a maternal subcutaneous dose of 30 mcg/kg/day). Cleft palate and fetal skeletal variations were observed in mouse fetuses at a dose approximately 0.1 times the MRHDID (on a mg/m^2 basis with a maternal subcutaneous dose of 45 mcg/kg/day). The mouse NOAEL was observed with a dose approximately 0.04 times the MRHDID (on a mg/m^2 basis with a maternal subcutaneous dose of 15 mcg/kg/day).

In an embryofetal development study with pregnant rates dosed by the inhalation route throughout the period of organogenesis, fluticasone propionate produced decrease fetal body weights and skeletal variations, in the presence of maternal toxicity, at a dose approximately 0.14 times the MRHDID (on a mg/m^2 basis with a maternal subcutaneous dose of 25.7 mcg/kg/day); however there was no evidence of teratogenicity. The NOAEL was observed with a dose

approximately 0.03 times the MRHDID (on a mg/m^2 basis with a maternal subcutaneous dose of 5.5 mcg/kg/day).

In an embryofetal development study in pregnant rabbits that were dosed by the subcutaneous route throughout organogenesis, fluticasone propionate produced reductions of fetal body weights, in the presence of maternal toxicity, at doses approximately 0.006 times the MRHDID and higher (on a mg/m^2 basis with a maternal subcutaneous dose of 0.57 mcg/kg/day). Teratogenicity was evident based upon a finding of cleft palate for one fetus at dose approximately 0.04 times the MRHDID (on a mg/m^2 basis with a maternal subcutaneous dose of 4mcg//kg/day). The NOAEL was observed in rabbit fetuses with a dose approximately 0.001 times the MRHDID (on a mg/m^2 basis with a maternal subcutaneous dose of 0.08 mcg/kg/day). Fluticasone propionate crossed the placenta following subcutaneous administration to mice and rats and oral administration to rabbits.

In a pre- and post-natal development study in pregnant rats dosed from late gestation through delivery and lactation (Gestation Day 17 to Postpartum Day 22), fluticasone propionate was not associated with decreases in pup body weight, and had no effects on developmental landmarks, learning, memory, reflexes, or fertility at doses up to 0.3 times the MRHDID (on a mg/m^2 basis with a maternal subcutaneous doses up to 50 mcg/kg/day).

8.2 Lactation

Risk Summary

There are no available data on the presence of fluticasone propionate in human milk, the effects on the breastfed infant, or the effects on milk production. Fluticasone is present in rat milk. Other corticosteroids have been detected in human milk. However, fluticasone propionate concentrations in plasma after inhaled therapeutic doses are low, and therefore, concentrations in human breast milk are likely to be correspondingly low *[see Clinical Pharmacology (12.3)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for and any potential adverse effects on the breastfed infant from XHANCE or from the underlying maternal condition.

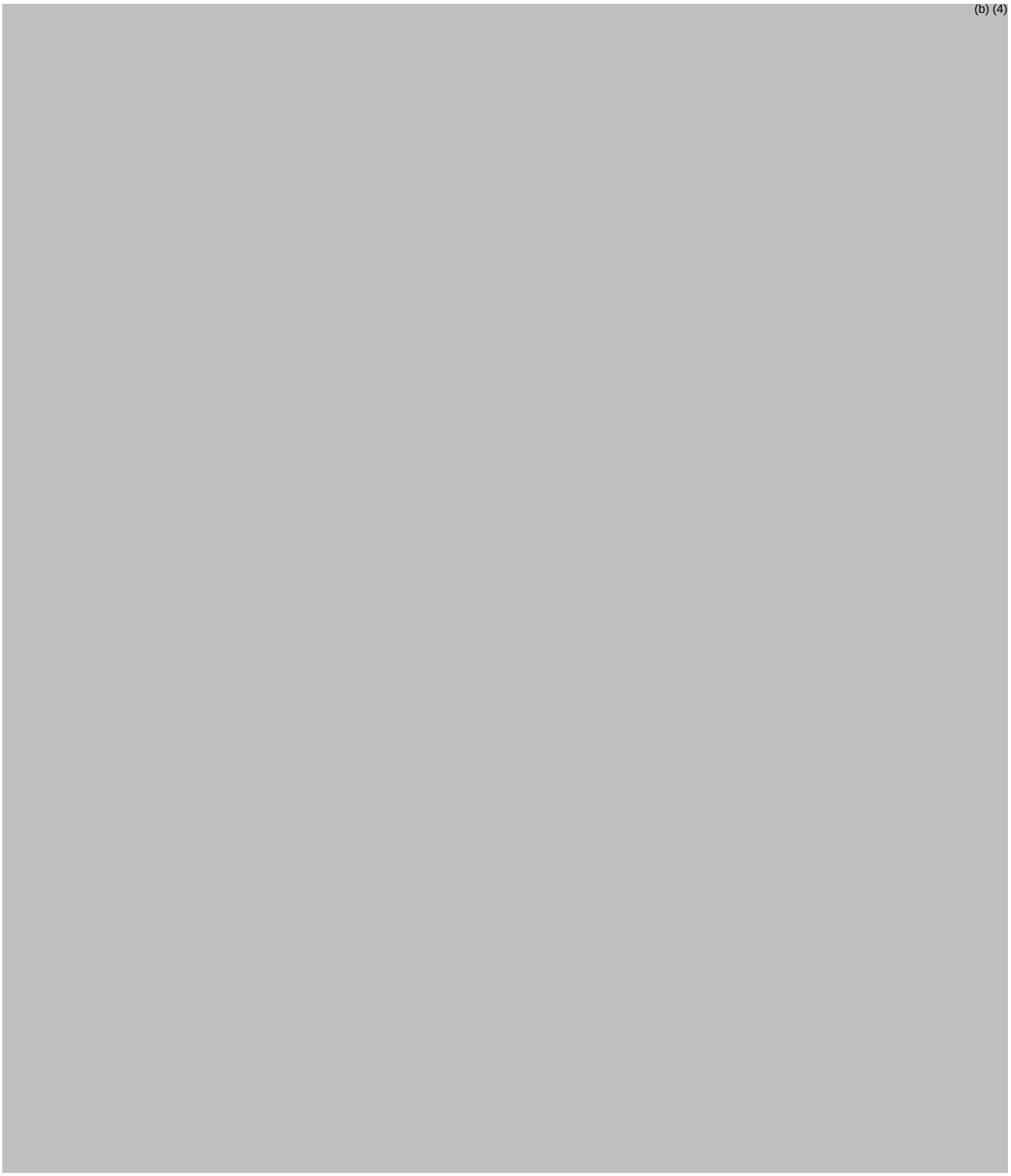
APPENDIX A – Applicant's Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)



2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

8.2 Lactation

Risk Summary

(b) (4), other corticosteroids have been detected in human milk. (b) (4)

Subcutaneous administration (b) (4) lactating rats (b) (4) tritiated fluticasone propionate at a dose approximately (b) (4) times the MRHDID for adults on a mg/m^2 basis resulted in measurable (b) (4) in milk. (b) (4) .

(b) (4)

17 PATIENT COUNSELING INFORMATION

PATIENT INFORMATION

Tell your healthcare provider about all of your health conditions, including if you:

- are pregnant or (b) (4) to become pregnant. It is not known if XHANCE may harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if XHANCE passes into your breast milk and if it can harm your baby.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CATHERINE A ROCA
07/21/2017

MIRIAM C DINATALE
07/21/2017

LYNNE P YAO
07/24/2017

CLINICAL INSPECTION SUMMARY

Date	June 2, 2017
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Cynthia Kleppinger, M.D., Acting Team Leader, for Janice Pohlman M.D., M.P.H., GCPAB Team Leader Kassa Ayalew, M.D., M.P.H. GCPAB Branch Chief Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Courtney McGuire, MD, M.D., Medical Officer Anthony Durmowicz, M.D., Cross-Discipline Team Leader Phuong Nina Ton, Senior Regulatory Project Manager Division of Pulmonary, Allergy and Rheumatology Products
NDA	209022
Applicant	OptiNose US, Inc.
Drug	intranasal fluticasone
NME	No
Therapeutic Classification	corticosteroid
Proposed Indication	Treatment of nasal (b) (4)
Consultation Request Date	January 30, 2017
Summary Goal Date	June 30, 2017
Action Goal Date	September 18, 2017
PDUFA Date	September 18, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Navratil and Albu) and the sponsor were selected by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) for inspection of Study OPN-FLU-NP-3101 and Study OPN-FLU-NP-3102, in support of NDA 209022. The study data derived from the two clinical sites and the sponsor are considered reliable in support of the requested indication.

The preliminary CDER regulatory classification for the sponsor is Voluntary Action Indicated (VAI). The preliminary regulatory classification of the inspections of Drs. Navratil and Albu is No Action Indicated (NAI).

2. BACKGROUND

To reduce inflammation and polyp size, the sponsor argues that the intranasal steroidal drug must reach the polyps in sufficient quantities. Sponsor's delivery device system, OPTINOSE fluticasone device, adopts an approach to intranasal drug administration which takes advantage of a closed-palate bi-directional exhalation delivery, in part, to address some of the problems of existing intranasal drug delivery systems for treatment of nasal polyps.

Two randomized clinical trials submitted in support of the applicant's NDA for the treatment of adult patients with (b) (4) nasal (b) (4) were inspected.

- **OPN-FLU-NP-3101** A 16-Week Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study Evaluating the Efficacy and Safety of Intranasal Administration of 100, 200, and 400 µg of Fluticasone Propionate Twice a Day (bid) Using a Novel Bi-directional Device in Subjects with Bilateral Nasal Polyposis Followed by an 8-week Open-label Extension Phase to Assess Safety
- **OPN-FLU-NP-3102** A 16-Week Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study Evaluating the Efficacy and Safety of Intranasal Administration of 100, 200, and 400 µg of Fluticasone Propionate Twice a Day (bid) Using a Novel Bi-directional Device in Subjects with Bilateral Nasal Polyposis Followed by an 8-week, Open-label Extension Phase to Assess Safety

For this NDA, CDER DPARP requested two foreign clinical sites and the sponsor for inspection. These sites principally enrolled large numbers of study subjects, had differential efficacy findings across clinical study sites, and other study risk as assessed by CDER DPARP.

Study OPN-FLU-NP-3101

Study OPN-FLU-NP-3101was a randomized, double-blind, placebo-controlled, parallel-group, multi-center study of intranasal fluticasone propionate in patients with bilateral nasal polyposis. The primary objective of the study was to compare the efficacy of intranasal administration of 100 µg, 200 µg, and 400 µg fluticasone (OPN-375) twice a day with placebo in subjects with bilateral nasal polyposis.

The co-primary endpoints were (1) a reduction of nasal congestion/obstruction symptoms over the seven days immediately prior to the Week 4 visit of the double-blind treatment phase, measured by the 7-day average of instantaneous morning (AM) diary symptom scores (ADS7-IA) and (2) reduction in total polyp grade (sum of scores from both nasal cavities) at Week 16 of the double-blind treatment phase as determined by a nasal polyp grading scale score measured by nasoendoscopy.

There were 323 study subjects enrolled and randomized using a 1:1:1:1 ratio to receive one of the four study treatments, with 282 subjects enrolling into the open-label extension phase. The study was conducted in 54 centers worldwide, with 54 investigators participating from six countries (Canada, Czech Republic, South Africa, Ukraine, United Kingdom, and United States). The first subject enrolled November 19, 2013 and the last subject completed August 6, 2015 (double-blind phase) and October 1, 2015 (open-label phase), respectively.

Study OPN-FLU-NP-3102

Study OPN-FLU-NP-3102 was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study of intranasal fluticasone propionate in patients with bilateral nasal polyposis. The primary objective of this study was to compare the efficacy of intranasal administration of 100 µg, 200 µg, and 400 µg of fluticasone (OPN-375) bid with placebo in subjects with bilateral nasal polyposis.

The co-primary endpoints were (1) reduction of nasal congestion/obstruction symptoms at the end of Week 4 of the double-blind treatment phase, measured by the 7-day average instantaneous morning diary symptom scores (ADS7-IA) and (2) reduction in total polyp grade (sum of scores from both nasal cavities) at Week 16 of the double-blind treatment phase as determined by a nasal polyp grading scale score measured by nasoendoscopy.

There were 323 subjects randomized using a 1:1:1:1 ratio to receive one of the four study treatments, with 299 subjects enrolling into the open-label extension phase. The study was conducted at 38 investigator sites in five countries (Poland, Romania, South Africa, Ukraine, and the United States). The first subject was enrolled October 30, 2013. The last subject completed May 11, 2015 (double-blind phase) and July 03, 2015 (open-label extension), respectively.

3. RESULTS (by site):

Name of Clinical Investigator/Sponsor Address	Protocol #/ Site #/# Subjects	Inspection Date	Classification
Pavel Navratil, M.D. Hospital Prostejov Otorhinolaryngology Department Mathonova 291/1 779 04 Prostejov Czech Republic	Protocol 3101 Site: 203 Subjects=25	May 15 to 19, 2017	Preliminary NAI
Silviu Albu, M.D. Hospital CF Cluj Napoca 16-18 Republicia 400015 Cluj Napoca Romania	Protocol 3102 Site: 407 Subjects=24	May 1 to 17, 2017	Preliminary NAI
OptiNose US, Inc. 1020 Stony Hill Road, Suite 300 Yardley, PA 19067	Sponsor for studies: Protocol 3101 Protocol 3102	May 15 to 26, 2017	Preliminary VAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data are unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Investigator

1. Pavel Navratil, M.D. /Study 3101/Site # 203

The inspection was conducted from May 15 to 19, 2017. A total of 30 subjects were screened, and 25 subjects were enrolled and randomized. One subject withdrew further participation from the study. Twenty four subjects completed the study. An audit of 20 randomized subjects' records enrolled at this site was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. No Form FDA 483 (Inspectional Observations) was issued.

2. Silviu Albu, M.D. /Study 3102/Site # 407

The inspection was conducted from May 1 to17, 2017. A total of 29 subjects were screened, and 24 subjects were enrolled and randomized. Twenty four study subjects completed the study. An audit of the 24 randomized subjects' records enrolled at this site was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection. No Form FDA 483 was issued.

Sponsor

3. OptiNose US, Inc.

This inspection was conducted from May 15 to 26, 2017.

The sponsor inspection included review of the following: regulatory site set up, financial disclosures, site management and monitoring, electronic Trial Master File (eTMF), functional services, and the Clinical Trial Management System (CTMS). Sites for which monitoring files were reviewed during the inspection: Sites 407, 203, 134, 515, 180, 302, 802, 312, and 705.

Monitoring plans and visits including study site closeout were reviewed; monitoring reports indicated that the sites received adequate periodic monitoring. IRB approvals, site study protocol deviations, serious adverse events and related monitoring reports were assessed, and oversight by the sponsor appeared to be adequate. There were no under-reporting of serious adverse events.

A one-item Form FDA 483 was issued at the end of the inspection. Specifically, an investigator at Site #515 who did not comply with the signed agreement, the general investigational plan and applicable regulatory requirements was not promptly brought into compliance. For example,

(a) Monitoring Visit Reports examined during the site audit indicated noncompliance over a period of several months at Site #515, including enrolling a subject that met exclusion criteria (Subject 515201) and destroying drug kits at the site instead of returning them to the sponsor as per protocol.
(b) The Certificate of Destruction document was not signed until 23 days after destruction, for nine unused and returned investigational product kits plus 30 used investigational product kits.

The above regulatory deficiencies observed at the sponsor site did not impact study subject safety.

The aforementioned regulatory deficiencies were not critical, and data integrity did not appear to be compromised. The sponsor maintained, in general, adequate oversight of the clinical trial.

{See appended electronic signature page}

Anthony Orencia, M.D., F.A.C.P.
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CONCURRENCE:

{See appended electronic signature page}

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Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
06/02/2017

CYNTHIA F KLEPPINGER
06/02/2017

KASSA AYALEW
06/02/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 209022	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: [redacted] (b) (4) (proposed) Established/Proper Name: Fluticasone Propionate Dosage Form: Nasal Spray Strengths: 93 mcg Route(s) of Administration: Intranasal		
Applicant: OptiNose US, Inc. Agent for Applicant (if applicable):		
Date of Application: November 18, 2016 Date of Receipt: November 18, 2016 Date clock started after Unacceptable for Filing (UN):		
PDUFA Goal Date: September 18, 2017	Action Goal Date (if different):	
Filing Date: January 17, 2017	Date of Filing Meeting: January 5, 2017	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☒ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Nasal [redacted] (b) (4)		
Type of Original NDA: AND (if applicable)	☐ 505(b)(1) ☒ 505(b)(2)	
Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☐ 505(b)(2)	
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)	

Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☒ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☒ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 110089	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.***	☒	☐		

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov)*: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☒	☐		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		

• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☒	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
NDA 021152	Cutivate Lotion 0.05%	NPP	January 16, 2018
NDA 205434	Flonase Allergy Relief	M-147	July 23, 2017

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

• If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement **[see 21 CFR 314.50(i)(1)(i)(C) and 314.54]**? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If no,** include template language in the 74-day letter. ***Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]*** ***Note: Pharmaceutical equivalents** are drug products in identical dosage forms and route(s) of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or	☒	☐		

dissolution rates.				
Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☐	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☐	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	
Forms and Certifications				
***Electronic** forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, **paper** forms and certifications with hand-written signatures must be included.* ***Forms** include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	

[1] http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☒	☐	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required***[3]	☐	☐		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829 htm

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837 htm

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☒ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☐	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☐	

[4] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☒	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☒	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☒	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:*** **Division of Pediatric and Maternal Health, 1/12/2017**	☒	☐	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):**	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** November 18, 2015	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐			

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 5, 2017

BACKGROUND: Optinose submitted a new drug application dated November 18, 2016 for the treatment of nasal [redacted] (b) (4) in patients 18 years of age or older.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Nina Ton	Y
	CPMS/TL:	Ladan Jafari	N
Cross-Discipline Team Leader (CDTL)	Tony Durmowicz		Y
Division Director	Badrul Chowdhury		Y
Division Deputy Director	Lydia Gilbert-McClain		N
Clinical	Reviewer:	Courtney McGuire	Y
	TL:	Tony Durmowicz	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Abir Absar	Y
	TL:	Bavna Saluja	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Feng Li	Y
	TL:	Shanti Gomatam Greg Levin	N Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Brett Jones	Y
	TL:	Tim Robison	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Craig Bertha	Y
	RBPM:	Florence Aisida	Y
• Drug Substance	Reviewer:	Jeffrey Medwid	N
• Drug Product	Reviewer:	Caroline Strasinger	Y
• Process	Reviewer:		
• Microbiology	Reviewer:	Joanne Wang	N
• Facility	Reviewer:	Cassandra Abellard	Y
• Biopharmaceutics	Reviewer:	Min Li/Kimberly Raines	N
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Nyedra Booker	Y
	TL:	Marcia Britt-Williams	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Taylor Burnett	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees			
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☐ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	☒ N/A
• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?	☐ YES ☐ NO
• If so, were the late submission components all submitted within 30 days?	☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Lydia Gilbert-McClain **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PHUONG N TON
01/26/2017

LADAN JAFARI
01/26/2017

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 209022

Application Type: NDA Type 5

Drug Name(s)/Dosage Form(s): Fluticasone Propionate Nasal Spray, 93 mcg

Applicant: OptiNose US, Inc.

Receipt Date: November 18, 2016

Goal Date: September 18, 2017

1. Regulatory History and Applicant's Main Proposals

Optinose submitted a new drug application dated November 18, 2016 for the treatment of nasal (b) (4) in patients 18 years of age or older.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

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4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

Selected Requirements of Prescribing Information

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

Selected Requirements of Prescribing Information

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.
Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

Selected Requirements of Prescribing Information

N/A 16. RMC pertains to only <u>five</u> sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

<u>Comment</u>:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

<u>Comment</u>:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

<u>Comment</u>:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

<u>Comment</u>:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

<u>Comment</u>:

Adverse Reactions in Highlights

NO 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

<u>Comment</u>: *Insert manufacturer's phone number*

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

<u>If a product **does not** have FDA-approved patient labeling</u>:

- **See 17 for PATIENT COUNSELING INFORMATION**

<u>If a product **has (or will have)** FDA-approved patient labeling</u>:

Selected Requirements of Prescribing Information

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "*[see Warnings and Precautions (5.2)]*."

Comment:

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PHUONG N TON
01/26/2017

LADAN JAFARI
01/26/2017