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APPLICATION NUMBER:

209022Orig1s000

NON-CLINICAL REVIEW(S)

Pharmacology and Toxicology Secondary Review for NDA 209022

Date
August 15, 2017

To
NDA 209022
XHANCE (OPN-375; fluticasone propionate intranasal spray)
OptiNose U.S., Inc.

From
Andrew Goodwin, PhD
Pharmacology-Toxicology Supervisor (Acting)
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

OptiNose submitted the present 505(b)(2) NDA application seeking approval of their intranasal fluticasone propionate (FP) product. The application references the previously approved FP products FLOVENT HFA (NDA 21433) and FLONASE (NDA 20121). The product is intended for the treatment of nasal polyps in adults 18 years of age or older at a total daily dose of 372 or 744 mcg FP.

No new nonclinical studies were conducted or requested to support the current NDA. The primary nonclinical reviewer, Dr. Brett Jones has 1) evaluated the safety of the proposed formulation; 2) assessed the local safety qualification of the 744 mcg per day intranasal dose of FP; 3) provided a toxicological assessment of extractables studies conducted with the container-closure system; and 4) provided labeling recommendations.

Dr. Jones provided the primary nonclinical review on July 28, 2017. I agree with the conclusions of Dr. Jones that there are no nonclinical safety concerns with the levels of excipients, impurities, and degradants in the proposed product. Further, I concur with Dr. Jones' conclusion that the local safety of the proposed intranasal dose of FP is qualified based on available nonclinical data and monitorability in the clinical setting. In addition, I concur with the recommended PLLR-compliant labeling language.

In addition, Dr. Jones provided a separate review dated August 14, 2017 covering the extractables assessment of the container closure system. I concur with Dr. Jones' conclusion that there are no nonclinical safety concerns related to the observed levels of the identified compounds.

There are no outstanding nonclinical issues. I concur with Dr. Jones' conclusion that NDA 209022 is recommended for approval from the pharmacology-toxicology perspective.

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

/s/

ANDREW C GOODWIN
08/15/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY SAFETY ASSESSMENT OF EXTRACTABLES AND LEACHABLES FOR XHANCE™ (OPN-375)

Application number:	NDA 209022
Supporting document/s:	SDN#1
Applicant's letter date:	November 16, 2016
CDER stamp date:	November 16, 2016
Product:	XHANCE™ (OPN-375) (Fluticasone propionate)
Indication:	Nasal (b) (4)
Applicant:	OptiNose U.S., Inc.
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer:	Brett Jones, PhD
Supervisor (Acting):	Andrew Goodwin, PhD
Division Director:	Badrul Chowdhury, MD, PhD
Project Manager:	Nina Ton, PharmD

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

The Sponsor submitted the present 505(b)(2) New Drug Application (NDA) 209,022 on November 16, 2016 to support the marketing approval of a fluticasone propionate multi-dose intranasal spray suspension using a proprietary bidirectional breath-powered exhalation delivery system. The OptiNose exhalation metered intranasal spray, proposed tradename XHANCE™, is being developed to treat nasal (b) (4) in adults 18 years of age or older at a total daily dose of 372 or 744 mcg/day fluticasone propionate. This review is a nonclinical safety evaluation of potential extractables for the XHANCE™ intranasal drug product.

The overall nonclinical pharmacology and toxicology evaluation, as well as labeling recommendations, was provided in a separate review dated July 28, 2017.

1.2 Brief Discussion of Nonclinical Findings

At this time, there are no safety concerns based on the results from the extractable studies.

2 Drug Information

2.1 Drug

CAS Registry Number
80474-14-2

Tradename
XHANCE™ (proposed)

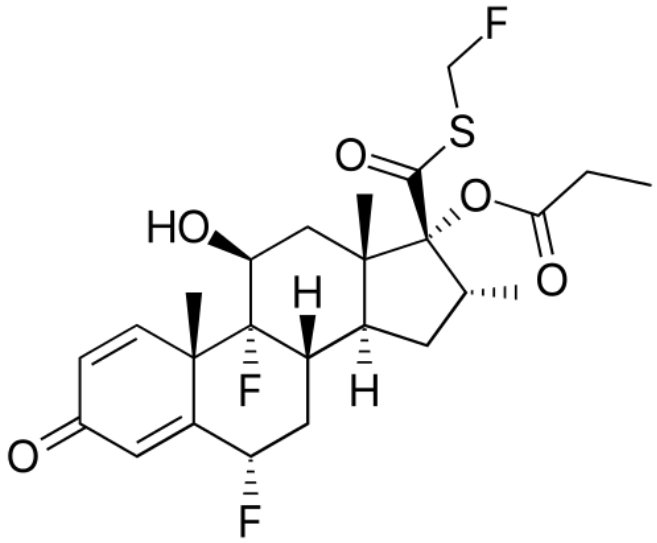
Generic Name
Fluticasone propionate

Code Name
OPN-375

Chemical Name
S-(fluoromethyl)6α,9-difluoro-11β-17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate

Molecular Formula/Molecular Weight
$C_{25}H_{31}F_3O_5S$ / 500.6 g/mole

Structure or Biochemical Description



Pharmacologic Class
Corticosteroid

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 110,089
NDA 20,121 – GSK, Flonase®
NDA 21,433 – GSK, Flovent® HFA
NDA 208798/208799: Teva, ArmonAir RespiClick®
NDA 21,077: GSK, Advair® Diskus®

2.3 Drug Formulation

The Sponsor's proposed drug product (i.e., XHANCE™ nasal spray, OPN-375), is a proprietary bidirectional breath-powered, multi-dose, exhalation delivery system containing an aqueous suspension of fluticasone propionate for the intranasal delivery of a metered spray of the active pharmaceutical ingredient.

The drug product formulation is a white milky suspension containing a (b) (4) per (b) (4) spray, the nominal volume of each actuation of the product. **The product delivers 93 mcg of fluticasone propionate from the mouthpiece per actuation.**

The composition of XHANCE™ intranasal spray is provided in the table below.

(Excerpt from Sponsor's submission)

Table 1. Components of OPN-375 formulation

Component	Function	Concentration (%w/w)	Amount per Spray[a] (µg)	Amount per Vial (mg)	Reference to Quality Standards
Fluticasone propionate	Drug substance	(b) (4)	93[b]	(b) (4)	USP/NF, Ph Eur (see *section 3.2.S.4.1*[c])
Polysorbate 80[d]	(b) (4)		(b) (4)		USP/NF, Ph Eur
Microcrystalline cellulose and carboxymethylcellulose sodium, [c, e]					USP/NF, Ph Eur (see *section 3.2.P.4.1*)
Benzalkonium chloride		0.02 (b) (4)			USP/NF, Ph Eur
EDTA disodium, dihydrate					USP/NF, Ph Eur
Dextrose					USP/NF, Ph Eur
(b) (4)					USP/NF, Ph Eur
					USP/NF, Ph Eur
Purified water					USP/NF, Ph Eur
(b) (4)				(b) (4)	

Ph Eur = European Pharmacopoeia;
USP/NF = United States Pharmacopeia/National Formulary.
[a] = Each spray is a (b) (4) (106 mg) (b) (4)

[c] = Complies with cited compendia plus additional tests to ensure drug product manufacturability and/or functionality; see referenced section.
[d] = Tradename (b) (4)
[e] = Tradename (b) (4)

2.4 Comments on Novel Excipients

There are no safety concerns with the excipients at the proposed maximum daily intranasal dose of 744 mcg (i.e., 8 sprays given as 2x93 mcg per nostril twice daily).

2.5 Comments on Extractables and Leachables Studies

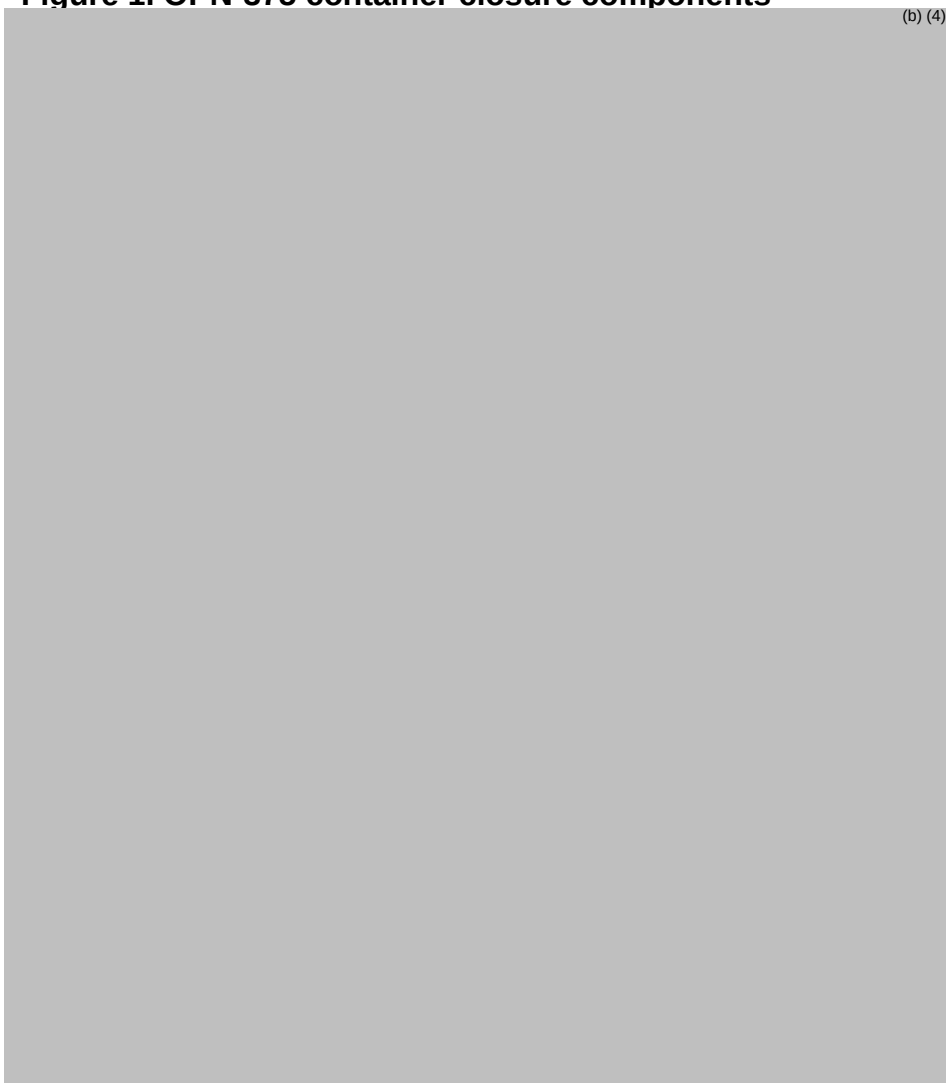
This review is a nonclinical safety evaluation of potential leachables for the XHANCE™ drug product. Described in this section are the studies and results; the nonclinical safety evaluation is included in the **Integrated Summary and Safety Evaluation** section.

The XHANCE™ drug product delivers drug using an exhalation drug delivery system. According to the Sponsor's report, it is composed of a pharmaceutical industry standard amber glass vial containing a suspension of fluticasone propionate, a standard metering spray pump, and plastic casework with a valve mechanism, an asymmetrically shaped sealing nosepiece, and flexible mouthpiece. The casework defines the drug delivery system's outer shape and includes the flexible mouthpiece and sealing nosepiece. Inside the delivery system, a nasal applicator extends from the metering pump to the tip of the nosepiece.

XHANCE™ is a multi-dose product, and the drug product container closure reservoir (glass vial and metering pump) is not intended to be removable from the device once assembled during the manufacturing process. XHANCE™ delivers 120 sprays, and the product cannot be refilled or reused after the original doses are dispensed. The components of the XHANCE™ container closure system are presented below.

(Excerpt from Sponsor's submission)

Figure 1. OPN-375 container closure components



(Excerpt from Sponsor's submission)

Figure 2. Cutaway diagram of the interior and operation of OPN-375 during pre-actuation with exhaled air against the closed mouthpiece valve (A), and exit of the

)

Extractables Testing Strategy: The Sponsor conducted extractable analyses of the drug contact parts of the container closure system including the nasal spray pump (consisting of (b) (4), glass vial, and applicator (including the (b) (4)). The studies were conducted to determine a semi-quantitative extractable profile of selected components in water, isopropanol, and hexane for the (b) (4) components and dilute nitric acid for the glass. The study utilized guidelines of Product Quality Research Institute (PQRI) best practices for extractable and leachable studies for orally inhaled and nasal products.

(Excerpt from Sponsor's submission)

Table 2. OPN-375 components assessed in the extractable study

Product Contact Component	Material of Construction
Nasal spray pump	(b) (4)
Glass vial	
Applicator	
	(b) (4)

The analytical testing performed on the packaging components during the extractable study included:

1. Organic extractables using high performance liquid chromatography coupled with photodiode array spectroscopy and mass spectroscopy (HPLC/PDA/MS)
2. Semi-volatile organic extractables using gas chromatography/mass spectroscopy (GC/MS) direct injection
3. Volatile organic extractables using GC/MS headspace analysis
4. Extractable metals by inductively-coupled plasma/optical emission spectroscopy (ICP/OES)
5. Non-volatile residue (NVR) with infrared spectroscopic evaluation (FTIR)

According to the Sponsor's report, the calculation of estimated and final Analytical Evaluation Threshold (AET) extractables was performed for critical components which are in continuous contact with the drug product and takes into consideration the safety concern threshold of (b) (4) mcg/day. A maximum of 8 doses per day can be administered, which equates to (b) (4) total doses per device, which was also considered in the AET calculations. An AET calculation was not performed for the glass bottle as the component was evaluated only for inorganic extractables (metals). A threshold of (b) (4) mcg/g of glass was used for inorganic extractables (metals).

According to the Sponsor's report, the weights of the components were determined by the laboratory. The weight and AET values determined for all components are provided in the table below.

(Excerpt from Sponsor's submission)

Table 3. Extractable threshold values

Sample ID	Component	Weight, g	Estimated AET, µg/g	Final AET, µg/g
1100024146	Applicator	[redacted]	[redacted]	[redacted]
1100024147				
1100024148				
1100024149				
1100024150				
1100024152				
1100024153				
1100024154				

Organic Extractables Assessment

The isopropanol and water extracts of the [redacted] components and their corresponding extraction blanks were analyzed directly. A 2mL aliquot of the hexane extracts of the [redacted] components and the corresponding extraction blank were evaporated to dryness at room temperature and the residues were reconstituted in 2 mL portions of acetonitrile for analysis. Both a UV-PDA chromatogram and a positive ion mass spectral total ion chromatogram were generated for each injection.

Semi-Volatiles Extractables Assessment

The isopropanol and hexane extracts of the [redacted] components and their corresponding blanks were analyzed directly. The water extracts of the [redacted] components were first extracted with an equal volume of methylene chloride since water is detrimental to the column and the overwhelming majority of GC-detectable extractables have a greater affinity for organic solvents than for water.

Volatiles Extractables Assessment

The vials were heated to 100°C for 30 minutes.

Elemental Extractables Assessment

The water extracts of the [redacted] components were acidified to about 1% with concentrated nitric acid. The 1% nitric acid extracts of the glass bottle were analyzed directly. The lower limit of quantification of the method was approximately [redacted] mcg/mL with the analysis of an LOQ standard; this corresponds to approximately [redacted] mcg/g of glass and to the calculated AET of the [redacted] components.

Non-Volatile Extractables Assessment

The extracts of the [redacted] components were evaluated for non-volatile residue (NVR). Each extract was first observed for presence of a precipitate. The contents of

the containers were evaporated to dryness and the weight of the residue in each container, or on each filter, was determined.

A summary of results of the extractables assessment is provided in the table below.

(Excerpt from Sponsor's submission)

Table 4. OPN-375 components extractable evaluation

Product Contact Component	Final AET (µg/g)	Extractable Assessment Results
Nasal spray pump (b) (4)	(b) (4)	Organic compounds: (b) (4) (b) (4) were observed above the AET of (b) (4) µg/g. Volatile compounds: no volatile compounds were observed in the headspace. Inorganics: (b) (4) were observed above the AET; all 3 (b) (4) were also observed in the extraction blank. FTIR evaluation of nonvolatile residue indicated the presence of (b) (4)
(b) (4)	(b) (4)	Organic compounds: (b) (4) (b) (4) and unknowns were observed above the AET of (b) (4) µg/g. Volatile compounds: (b) (4) (b) (4) were observed in the headspace. The largest peaks were identified as (b) (4) (b) (4) Inorganics: (b) (4) were observed above the AET; all 3 (b) (4) were also observed in the extraction blank although (b) (4) was observed at levels in the sample extracts roughly twice that found in the blank. FTIR evaluation of nonvolatile residue indicated the presence of (b) (4)
Body: (b) (4)	(b) (4)	Organic compounds: (b) (4) (b) (4) (b) (4) and unknowns were observed above the AET of (b) (4) µg/g. Volatile compounds: (b) (4) (b) (4) were observed in the headspace. The largest peaks were identified as (b) (4) Inorganics: (b) (4) observed above the AET; all 3 (b) (4) were also observed in the extraction blank. FTIR evaluation of nonvolatile residue indicated the presence of (b) (4)

Nasal spray pump (continued)	(b) (4)	(b) (4)	Organic compounds: (b) (4) were observed above the AET of (b) (4) µg/g. Volatile compounds: (b) (4) were observed in the headspace. All (b) (4) peaks were about the (b) (4) Inorganics: (b) (4) were observed above the AET; all 3 (b) (4) were also observed in the extraction blank. FTIR evaluation of nonvolatile residue suggested (b) (4)
	(b) (4)	(b) (4)	Organic compounds: (b) (4) were observed above the AET of µg/g. Volatile compounds: (b) (4) were observed in the headspace. The largest peak was identified as (b) (4) Inorganics: (b) (4) were observed above the AET; all 3 (b) (4) were also observed in the extraction blank. FTIR evaluation of nonvolatile residue suggested (b) (4)

Nasal spray pump (continued)	[redacted]	[redacted]	Organic compounds: [redacted] were observed above the AET of [redacted] µg/g. Volatile compounds: 1 peak identified as [redacted] was observed in the headspace. Inorganics: [redacted] were observed above the AET. [redacted] were also observed in the extraction blank at levels similar to those found in the sample extracts. While [redacted] was observed in the blank, the levels observed in the sample extracts were much higher. FTIR evaluation of nonvolatile residue indicated the presence of [redacted] and [redacted]
Glass vial	Type 1 [redacted]	Not applicable[a]	Inorganics [redacted] were observed above [redacted] µg/g
Applicator	[redacted]	[redacted]	Organic compounds [redacted] and unknowns were observed above the AET of [redacted] µg/g. Volatile compounds: [redacted] were observed in the headspace. The largest peaks were identified as [redacted] Inorganics: [redacted] were observed above the AET; all 3 [redacted] were also observed in the extraction blanks. FTIR evaluation of nonvolatile residue suggested a [redacted]

AET = analytical evaluation threshold; FTIR = fourier transform infrared spectroscopy.
[a] = The AET calculations were not performed for the glass vial as this component was evaluated only for inorganic extractable [redacted] and a threshold of [redacted] µg/g of glass was established.

According to the Sponsor's report, a priority score was assigned to each substance based on its toxicity, solubility, content per part, contact duration, exposure temperature, and patient contact. The Sponsor considered the majority of substances as low risk. The identification of [redacted] extracted from the [redacted] was regarded as a potential concern. The level of [redacted] slightly exceeded the AET threshold of [redacted] mcg/g, with measured values between [redacted] and [redacted] mcg/g. In addition, several organic compounds and volatile compounds were identified as extractables above the

AET threshold in the (b) (4) and (b) (4) of the nasal spray pump. A summary of semi-quantitated extractable compounds above the AET threshold that were detected in the XHANCE™ drug product components is shown in the table below.

Table 5. Semi-quantitative extractable results for XHANCE™ drug product components

Compound	Component	Maximum Extractable Concentration (mcg/g)	Potential Maximum Human Exposure[A] (mcg/day)
(b) (4)	(b) (4)	(b) (4)	(b) (4)

Exposures (mcg/day) were calculated from the extractables data by multiplying the extractable amount (mcg/g) by the approximate weight of the formulation per inhaler ((b) (4) and the maximum number of actuations per day (8/day), then dividing by the total number of actuations per inhaler (120/inhaler).

3 Studies Submitted

3.1 Studies Reviewed

Title
Extractables Evaluation of Components of OptiNose Nasal Delivery Device (Report No. 2011001511 Rev 1)
Toxicity Profile and Risk Assessment for: (b) (4)

11 Integrated Summary and Safety Evaluation

This review provides a safety assessment of extractables from the primary closed container system for the XHANCE™ drug product, based on data submitted by the Sponsor and other available information. The sponsor did not submit any leachables studies; therefore the safety evaluation based on the extraction studies represents a 'worst-case' scenario assessment. The multi-dose product will be administered by the intranasal route.

In general, for leachable evaluations, compounds with expected patient exposure below the PQRI Thresholds of 5 mcg/day (for sensitizer and irritants, non-genotoxic/non-carcinogen) and 1.5 mcg/day (for compounds with genotoxic/carcinogenic potential) were considered qualified for safety. [1]

[1] Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products. Product Quality Research Institute. August 2006.

Extractables Assessment

An extractables assessment was conducted on the drug contact parts of the container closure system including the nasal spray pump (consisting of the [redacted]), glass vial, and applicator (including the [redacted] The studies were conducted to determine a semi-quantitative extractable profile of selected components in water, isopropanol, and hexane for the [redacted] components and dilute nitric acid for the glass. The study utilized guidelines of Product Quality Research Institute (PQRI) best practices for extractable and leachable studies for orally inhaled and nasal products.

Extractable studies on the [redacted] identified [redacted] at levels slightly above the calculated AET of [redacted] mcg/g. According to the Sponsor's report, the [redacted] of the spray pump is not in contact with the formulation prior to priming and therefore although [redacted] was extracted, this cannot leach out of the formulation during storage before use. [redacted] may only leach out of the [redacted] during the in-use life of the product, which is [redacted] days after initial priming. The [redacted] of the pump is also not a patient contact part. The reported level of [redacted] from leachable studies was [redacted] mcg/mL and the maximum amount of nasal administration of the drug product would be approximately [redacted] mL; the resultant potential exposure to [redacted] would therefore be [redacted] mcg/day. [redacted] is a [redacted] and under physiological and other conditions releases [redacted]. At this time, given the worst-case exposure is ~[redacted]-fold below the NIOSH threshold level and [redacted]-fold below the dose associated with a minimal increase in cancer risk, as well as its intermittent administration (i.e., less than a lifetime exposure), [redacted] is considered qualified from the nonclinical perspective. In written responses to a Type C (CMC Only) Meeting dated July 21, 2015, the agency agreed that given the nature of contact with the formulation presented by the [redacted] and the results of the toxicological evaluation, monitoring [redacted] levels during stability testing and performing an in-use study was not necessary.

[redacted]

Extractable studies on the [redacted] identified [redacted] at levels above the calculated AET of [redacted] mcg/g. The highest level of [redacted] observed was [redacted] mcg/g; the resultant potential exposure to [redacted] would be approximately [redacted] mcg/day. [redacted] is a [redacted]. No substance-specific organ toxicity was observed after repeated administration in animals. Repeated oral uptake of [redacted] did not cause substance-related effects. The substance was not mutagenic or genotoxic in studies with mammals. No carcinogenic effects were observed in long term studies with rats and mice in which the substance was given as feed. No U.S. government reference limits are available, but a European Union (EU) derived no-effect level (DNEL) of [redacted] mg/m^3 was reported (long-term inhalation exposure for consumer).[4] Adjusting for a human daily respiratory volume of 28,800 L (per ICH Q3C), this value corresponds to [redacted] mg/day. Given the lack of observed toxicity and the > [redacted] x safety margin compared to the DNEL, [redacted] is considered qualified from the nonclinical perspective.

Extractable studies on the [redacted] identified [redacted] at levels above the calculated AET of [redacted] mcg/g. The highest level of [redacted] observed was [redacted] mcg/g; the resultant potential exposure to [redacted] would be approximately [redacted] mcg/day. [redacted], similar to [redacted], is [redacted] n repeat-dose toxicity studies, the substance may cause liver damage after repeated ingestion of high doses. The substance was not mutagenic or genotoxic. No carcinogenic effects were observed in long term studies with rats and mice in which the substance was given as feed. No U.S. government reference limits are available, but an EU DNEL of [redacted] mg/m^3 was reported (long-term inhalation exposure for consumer). [5] Adjusting for a human daily respiratory volume of 28,800 L (per ICH Q3C), this value corresponds to [redacted] mg/day. Given the lack of observed toxicity and the > [redacted] x safety margin compared to the DNEL [redacted] is considered qualified from the nonclinical perspective.

Extractable studies on the [redacted] identified [redacted] at levels above the calculated AET of [redacted] mcg/g. The highest level of [redacted] observed was [redacted] mcg/g; the resultant potential exposure to [redacted] would be approximately [redacted] mcg/day. [redacted] is a [redacted] It is used to [redacted]. No substance-specific organ toxicity was observed after repeated administration in animals. Repeated oral uptake of [redacted] did not cause any adverse effects. The substance was not mutagenic or genotoxic in studies with mammals. No carcinogenic effects were observed in long term studies with rats and mice in which the substance was given as feed.[6] The U.S. EPA Chemistry Dashboard reports a [redacted] /kg/day NOAEL in a sub-chronic rodent toxicology study.[7] A corresponding PDE of [redacted] mg per day was

[redacted]

calculated.[8] While the PDE was calculated based on oral toxicology data, given the lack of observed toxicity and the > (b) (4) x safety margin, (b) (4) is considered qualified from the nonclinical perspective.

Extractable studies on the (b) (4) identified (b) (4) at levels above the calculated AET of (b) (4) mcg/g. The highest level of (b) (4) observed was (b) (4) mcg/g; the resultant potential exposure to (b) (4) would be approximately (b) (4) mcg/day. (b) (4) is a (b) (4) . (b) (4) was administered to rats and mice in a lifetime bioassay sponsored by the (b) (4) Extremely high feed concentrations ((b) (4)) caused an increased incidence of liver tumors in female mice only. Previous long term feeding studies in rats and dogs did not detect tumors. Further studies have shown that the liver tumors observed in mice probably arose from (b) (4) effect on liver biochemistry.[9] (b) (4) is not genotoxic.[10] Regulatory guidelines on (b) (4) levels are available for the oral route of administration, including an EPA oral reference dose (RfD) of (b) (4) mg/kg (~ (b) (4) mg/day) and an FDA limit (b) (4) ((b) (4)). Given the large safety margins, the observed level of (b) (4) is considered qualified from the nonclinical perspective.

The sponsor's extractables studies identified various compounds that could be present in the drug product under a 'worst-case' scenario. Due to the: 1) semi-quantitative nature of the extractables studies, (2) lack of direct contact of certain components with the formulation, (3) intermittent patient use of the drug product, and 4) available toxicological data summarized above, the organic and volatile extractable compounds identified above the calculated AET thresholds are not considered a safety risk at this time.

(b) (4)

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/s/

BRETT R JONES
08/14/2017

ANDREW C GOODWIN
08/14/2017
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 209022
Supporting document/s:	SDN #1; SDN#6
Applicant's letter date:	November 18, 2016
	March 16, 2017
CDER stamp date:	November 18, 2016
	March 16, 2017
Product:	XHANCE™ (OPN-375)
	(Fluticasone propionate)
Indication:	Nasal (b) (4)
Applicant:	OptiNose U.S., Inc.
Review Division:	Division of Pulmonary, Allergy, and
	Rheumatology Products
Reviewer:	Brett Jones, PhD
Supervisor (acting):	Andrew Goodwin, PhD
Division Director:	Badrul Chowdhury, MD, PhD
Project Manager:	Nina Ton, PharmD

Template Version: September 1, 2010

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Any information or data necessary for approval of NDA 209022 that OptiNose US, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 209022.

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1 Executive Summary

1.1 Introduction

The Sponsor submitted the present 505(b)(2) application to support the development of a fluticasone propionate multi-dose intranasal spray suspension using a proprietary bidirectional breath-powered exhalation delivery system. Fluticasone propionate (Fp) is the active pharmaceutical ingredient (API) in multiple FDA-approved products delivered via the inhalation or intranasal routes of administration. These include the two reference listed drugs for the current application, FLOVENT® HFA (DPARP; Approval Action on May 14, 2004) and FLONASE® (DPARP; Approval Action on October 19, 1994). The Optinose exhalation metered intranasal spray (proposed tradename XHANCE) contains the same active ingredient as the reference listed drugs FLOVENT® HFA (i.e., marketed at strengths of 44, 110, and 220 mcg BID) and FLONASE® (i.e., marketed at a strength of 50 mcg BID). XHANCE is proposed to treat nasal polyps in adults 18 years of age or older at a total daily dose of 372 or 744 mcg Fp.

1.2 Brief Discussion of Nonclinical Findings

The Sponsor refers to the Reference Listed Drugs, FLONASE® and FLOVENT® HFA, marketed under NDA 20,121 and NDA 21,433, respectively. The listed drugs utilize the same API. FLONASE® nasal spray is approved for the management of nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in patients 4 years of age and older via the oral inhalation route. FLOVENT® HFA is approved for the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older and treatment of asthma for patients requiring oral corticosteroid therapy via the oral inhalation route. For this submission, the Sponsor is proposing XHANCE™ as an inhaled corticosteroid for the treatment of (b) (4) nasal (b) (4) in patients 18 years of age and older.

There is a complete nonclinical program for fluticasone propionate. No new nonclinical pharmacology or toxicology studies were conducted or required to directly support the safety of fluticasone propionate. Based upon the Agency's previous findings of safety and efficacy for the reference listed drugs, FLONASE® and FLOVENT® HFA, and the public literature, there is sufficient information from the nonclinical perspective to recommend the approval of NDA 209,022.

1.3 Recommendations

1.3.1 Approvability

NDA 209,022 is recommended for approval from the nonclinical perspective. The label should be modified as shown below.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

For this 505(b)(2) submission, the Sponsor originally provided a draft label for XHANCE™ based upon the approved product labels of the reference listed drugs, FLONASE® and FLOVENT® HFA previously approved by DPARP. This draft label did not comply with the Pregnancy and Lactation Labeling Rule (PLLR) format. On March 16, 2017, the Sponsor provided a revised draft label of XHANCE™ in compliance with PLLR format.

The Established Pharmacologic Class (under Indication and Usage in the Highlights of Prescribing Information), Section 8.1, Section 8.2, Section 12.1, and Section 13 were reviewed. See the recommended labeling for the nonclinical section of the product label below.

The Reviewer's recommended labeling is shown below. Additions are shown as underlined text and deletions are shown as strikethrough ~~text~~ with respect to the Sponsor's proposed XHANCE™ label.

XHANCE™

(b) (4)

(b) (4) is a corticosteroid indicated:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4)

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 mcg/m^2 basis (b) (4) 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 on a mcg/m^2 basis [*see* (b) (4) *Data*]. Experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. (b) (4)

The estimated risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriages in clinically recognized pregnancies (b) (4) is 2% to 4% and 15% to 20%, respectively.

(b) (4)

(b) (4)

Data

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 (b) (4) equivalent to the MRHDID (on a mcg/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 (b) (4)4 times the MRHDID (on a mcg/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. (b) (4)3 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 45 mcg/kg/day). The mouse NOAEL was observed with a dose approximately 0.1 (b) (4) times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 15 mcg/kg/day).

In an embryofetal development study with pregnant rats dosed by the inhalation route throughout the period of 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 MRHDID (on a mcg/m^2 basis with a maternal inhalation dose of 25.7 mcg/kg/day); however, there was no evidence of teratogenicity. The NOAEL was observed with a dose approximately 0. (b) (4)1 times the MRHDID (on a mcg/m^2 basis with a maternal inhalation 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 0.0 (b) (4)2 times the MRHDID and higher (on a mcg/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 1 fetus at a dose approximately 0.1 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 4 mcg/kg/day). The NOAEL was observed in rabbit fetuses with a dose approximately 0.002 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 0.08 mcg/kg/day). (b) (4)

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.[(b) (4)]7 times the MRHDID (on a mcg/m^2 basis with 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 child, or the effects on milk production. Other corticosteroids have been detected in human milk. However, fluticasone propionate concentrations in plasma after ~~orally~~ inhaled therapeutic doses are low, and therefore, concentrations in human breast milk are likely to be correspondingly low [see *Clinical Pharmacology (12.3)*]. [(b) (4)] The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for [(b) (4)] XHANCE and any potential adverse effects on the breastfed child from [(b) (4)] XHANCE or from the underlying maternal condition.

Data

[(b) (4)]

Subcutaneous administration of tritiated fluticasone propionate at a dose in lactating rats approximately 0.1[(b) (4)] times the MRHDID for adults (on a mcg/m^2 basis) resulted in measurable levels in milk. [(b) (4)]

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fluticasone propionate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. Fluticasone propionate has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor that is 18 times that of dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results. The clinical significance of these findings is unknown.

The precise mechanism through which fluticasone propionate affects nasal polyps and associated inflammatory symptoms is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (eg, mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. The anti-inflammatory action of corticosteroids contributes to their efficacy. In 7 trials in adults, fluticasone propionate nasal spray decreased nasal mucosal eosinophils in 66% of patients (35% for placebo) and basophils in 39% of patients (28% for placebo). In addition, studies suggest that carbon dioxide, which is present in the exhaled breath delivered into the nose through the device, may influence inflammatory mediator activity and neuropeptide activity, possibly through mechanisms of action that also include removal of nitric oxide, change in pH, or positive pressure. The direct relationship of these findings to long-term symptom relief is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1000 mcg/kg (approximately (b) (4) 7 times the MRHDID for adults on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (b) (4) (b) (4) approximately equivalent to the MRHDID for adults on a mcg/m basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the in vivo mouse micronucleus test.

Fertility and reproductive performance were unaffected in male and female rats at subcutaneous doses up to 50 mcg/kg (approximately 0. (b) (4) 7 times the MRHDID (b) (4) for adults on a mcg/m^2 basis).

(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number
80474-14-2

Tradename
XHANCE™ (proposed)

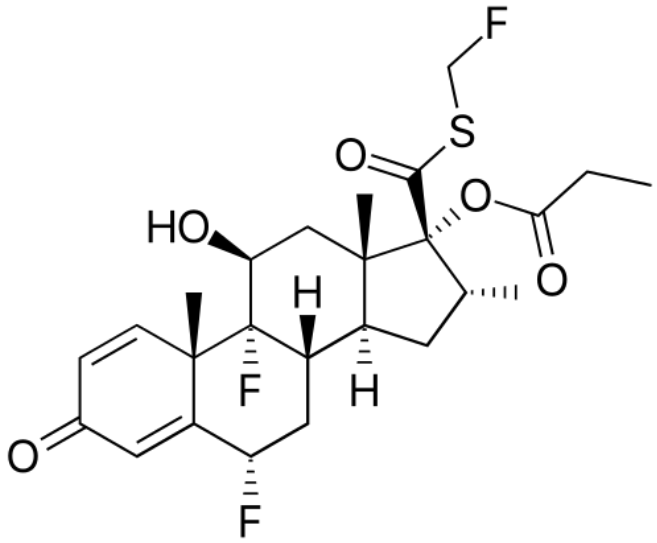
Generic Name
Fluticasone propionate

Code Name
OPN-375

Chemical Name
S-(fluoromethyl)6α,9-difluoro-11β-17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate

Molecular Formula/Molecular Weight
$C_{25}H_{31}F_3O_5S$ / 500.6 g/mole

Structure or Biochemical Description



Pharmacologic Class
Corticosteroid

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 110,089
NDA 20,121 – GSK, Flonase®
NDA 21,433 – GSK, Flovent® HFA
NDA 208798/208799: Teva, ArmonAir RespiClick®
NDA 21,077: GSK, Advair® Diskus®

2.3 Drug Formulation

The Sponsor's proposed drug product (i.e., XHANCE™ nasal spray, OPN-375), is a proprietary bidirectional breath-powered, multi-dose, exhalation delivery system containing an aqueous suspension of fluticasone propionate for the intranasal delivery of a metered spray of the active pharmaceutical ingredient.

The drug product formulation is a white milky suspension containing a (b) (4) per (b) (4) spray, the nominal volume of each actuation of the product. **The product delivers 93 mcg of fluticasone propionate from the mouthpiece per actuation.** OPN-375 has a net fill volume of 16 mL that delivers 120 sprays after initial priming. The drug product container closure reservoir (glass vial and metering pump) is not intended to be removable from the device after it is assembled during the manufacturing process and the product cannot be refilled or reused after the original doses are dispensed.

(Excerpt from Sponsor's submission)

Table 1. Components of OPN-375 formulation

Component	Function	Concentration (%w/w)	Amount per Spray[a] (µg)	Amount per Vial (mg)	Reference to Quality Standards
Fluticasone propionate	Drug substance	(b) (4)	93[b]	(b) (4)	USP/NF, Ph Eur (see *section 3.2.S.4.1*[c])
Polysorbate 80[d]	(b) (4)		(b) (4)		USP/NF, Ph Eur
Microcrystalline cellulose and carboxymethylcellulose sodium, [c, e]					USP/NF, Ph Eur (see *section 3.2.P.4.1*)
Benzalkonium chloride		0.02			USP/NF, Ph Eur
EDTA disodium, dihydrate		(b) (4)			USP/NF, Ph Eur
Dextrose					USP/NF, Ph Eur
(b) (4					USP/NF, Ph Eur
					USP/NF, Ph Eur
Purified water					USP/NF, Ph Eur
(b) (4)				(b) (4)	

Ph Eur = European Pharmacopoeia;
USP/NF = United States Pharmacopeia/National Formulary.
[a] = Each spray is a (b) (4) (106 mg). (b) (4)

[c] = Complies with cited compendia plus additional tests to ensure drug product manufacturability and/or functionality; see referenced section.
[d] = Tradename (b) (4)
[e] = Tradename (b) (4)
(b) (4)

Device: OPN-375 delivers drug using an exhalation drug delivery system. It is composed of an amber glass vial containing a suspension of fluticasone propionate, a standard metering spray pump, and plastic casework with a valve mechanism, an asymmetrically shaped sealing nosepiece, and a flexible mouthpiece. The casework

defines the drug delivery systems outer shape and includes the flexible mouthpiece and sealing nosepiece. Inside the delivery system, a nasal spray applicator extends from the metering pump to the tip of the nosepiece (see figures below). According to the Sponsor's summary, the OPN-375 drug delivery system includes a mouthpiece and sealing nosepiece, as part of a mechanism that enables use of the patient's exhaled breath to naturally seal closed the soft palate and to facilitate efficient and targeted delivery of drug to the nasal cavity through a sealing nosepiece.

The Sponsor conducted an extractables and leachables assessment of the OPN-375 intranasal delivery device; which will be the subject of a separate toxicological review.

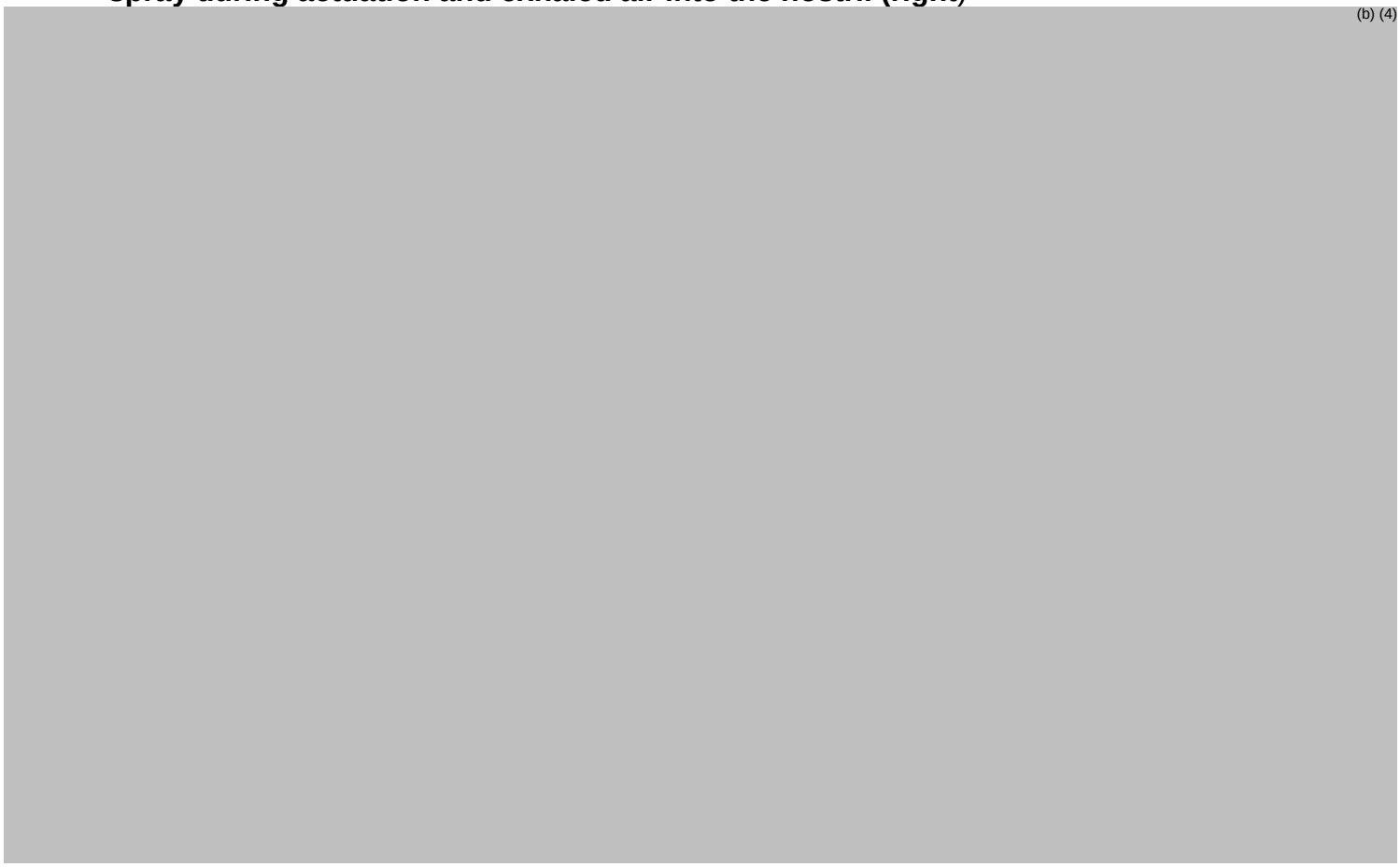
(Excerpt from Sponsor's submission)
Figure 1. View of assembled OPN-375 (without cap)

(Excerpt from Sponsor's submission)

Figure 2. OPN-375 container closure components

(Excerpt from Sponsor's submission)

Figure 3. Cutaway diagram of the interior and operation of OPN-375 during pre-actuation with exhaled air against the closed mouthpiece valve (A), and exit of the spray during actuation and exhaled air into the nostril (right)



2.4 Comments on Novel Excipients

There are no safety concerns with the excipients at the proposed maximum daily intranasal dose of 744 mcg (i.e., 8 sprays given as 2x93 mcg per nostril twice daily). All of the excipients in the formulation are covered by levels in currently approved intranasal products.

2.5 Comments on Impurities/Degradants of Concern

The assigned CMC reviewers for the drug product and drug substance stated that there were no impurity issues. As such there were no concerns from a CMC perspective.

A listing of potential impurities/degradants in the proposed drug product is provided in the table below. All the impurities originate from the drug substance. The proposed degradant levels for the drug product are being controlled below the ICH Q3B qualification threshold (i.e., 1.0%).

(Excerpt from Sponsor's submission)

Table 2. Drug-related substances in OPN-375

Drug Related Substances Name	Structure	Control Specification in Drug Specification	Justification
(b) (4)		NMT (b) (4)%	ICH guideline for qualification threshold is 1.0%
(b) (4)		NMT (b) (4)%	Conforms to USP monograph
(b) (4)		NMT (b) (4)%	Conforms to USP monograph
(b) (4)		NMT (b) (4)%	Conforms to USP monograph

EP = European Pharmacopeia; ICH = International Conference on Harmonization; NMT = not more than (b) (4)
USP = United States Pharmacopeia.

At the maximum daily dose of XHANCE™ (744 mcg/day), an impurity level (e.g., (b) (4)) of not more than (b) (4)% would correlate to an exposure of (b) (4) mcg/day.

2.6 Proposed Clinical Population and Dosing Regimen

XHANCE™ (fluticasone propionate, 93 mcg) nasal spray suspension for exhalation drug delivery is proposed for the treatment of (b) (4) nasal (b) (4) in patients 18 years of age or older.

Adults (18 years of age or older): 1 (b) (4) spray (93 mcg of fluticasone propionate) (b) (4) nostril twice daily (total daily dose, 372 mcg). (b) (4) 2 (b) (4) sprays (b) (4) (b) (4) nostril twice daily (total daily dose, 744 mcg). Total daily (b) (4) should not exceed 2 sprays in each nostril twice daily (total dose, 744 mcg).

The proposed maximum intranasal daily dose of Fluticasone propionate (744 mcg/day) does not exceed that of the reference listed drug FLOVENT® HFA (1760 mcg/day). However, it does exceed the maximum daily intranasal dose of FLONASE® nasal spray (200 mcg/day).

2.7 Regulatory Background

At a pre-IND meeting on December 20, 2010 (refer to meeting minutes dated January 20, 2011), the sponsor asked the Agency to confirm that no new toxicology studies would be required for their product (proposed dose up to (b) (4) mcg per day). The Agency did not request any additional Fp local toxicity data for the proposed product.

In a preliminary response to pre-IND meeting materials, the Agency noted that at the proposed maximum daily clinical dose of (b) (4) mcg fluticasone propionate, the level of the excipient dextrose appeared to be (b) (4)-fold the levels found in approved products for nasal inhalation and requested justification to support the safety of intranasal dextrose at this level. In an email communication dated December 19, 2011, the Sponsor stated the formulation for Beconase AQ contains (b) (4)% (w/w) dextrose concentration and the approved dosing is up to 8 sprays/day, making the exposure to dextrose equivalent with the proposed high dose of XHANCE™ (i.e., (b) (4) mcg). In addition, the Sponsor stated that the XHANCE™ dose is administered BID and the total daily exposure is divided into two parts spread over a 12-hr interval. The Agency agreed that the information provided was sufficient and no further information was needed regarding the levels of dextrose in the proposed product. The Sponsor was also requested to provide structures of impurities and degradants and any that were found to possess structural alerts for genotoxicity should be at or below acceptable qualification thresholds per the Draft Genotoxic Impurities Guidance. For an NDA submission, the Sponsor was requested to provide a safety qualification for leachables and extractables

XHANCE™ was developed under IND 110089 submitted on June 18, 2012.

At a pre-NDA meeting on November 18, 2015 (refer to meeting minutes dated December 3, 2015), the Agency reiterated that no additional toxicology data would be required to support the NDA submission.

On September 18, 2016 OptiNose US, Inc., submitted a New Drug Application (NDA) for XHANCE™ pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The NDA referred to the Listed Drugs, FLONASE®, marketed under GlaxoSmithKline NDA 20,121 (approved October 19, 1994, DPARP) and FLOVENT® HFA, marketed under GlaxoSmithKline NDA 21,433 (approved May 14, 2004, DPARP). The proposed indication was for the treatment of (b) (4) nasal (b) (4) in patients 18 years of age and older.

3 Studies Submitted

3.1 Studies Reviewed

No nonclinical studies were submitted or required for XHANCE™.

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

Pharmacology and Toxicology Review of IND 110,089 dated July 11, 2012.

4 Pharmacology

4.1 Primary Pharmacology

No primary pharmacology studies were submitted or required in the present 505(b)(2) submission.

4.2 Secondary Pharmacology

No secondary pharmacology studies were submitted or required in the present 505(b)(2) submission.

4.3 Safety Pharmacology

No safety pharmacology studies were submitted or required in the present 505(b)(2) submission.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No PK/ADME studies were submitted or required in the present 505(b)(2) submission.

5.2 Toxicokinetics

No TK studies were submitted or required in the present 505(b)(2) submission.

6 General Toxicology

6.1 Single-Dose Toxicity

No single-dose toxicity studies were submitted or required in the present 505(b)(2) submission.

6.2 Repeat-Dose Toxicity

No repeat-dose toxicity studies were submitted or required in the present 505(b)(2) submission.

7 Genetic Toxicology

No genetic toxicology studies were submitted or required in the present 505(b)(2) submission.

8 Carcinogenicity

No carcinogenicity studies were submitted or required in the present 505(b)(2) submission.

9 Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies were submitted or required in the present 505(b)(2) submission.

10 Special Toxicology Studies

No special toxicology studies were submitted or required in the present 505(b)(2) submission.

11 Integrated Summary and Safety Evaluation

OptiNose US Inc., has submitted a 505(b)(2) NDA for fluticasone propionate intranasal spray suspension using a proprietary multi-dose, bidirectional breath-powered exhalation delivery system. OptiNose U.S. Inc., is proposing the XHANCE™ drug product for the treatment of (b) (4) nasal (b) (4) in patients 18 years of age or older. The product will be administered via the intranasal route.

The Sponsor referenced the listed drugs, FLONASE® (marketed under NDA 20,121 and utilizes the same API) and FLOVENT® HFA (marketed under NDA 21,433 and utilizes the same API), to support the safety and efficacy of fluticasone propionate intranasal spray for the proposed indication and route of administration. There is a complete

nonclinical program for Fp conducted with the reference products. No nonclinical studies were conducted or required to support the safety of XHANCE™.

The Sponsor is proposing intranasal doses of fluticasone propionate (744 mcg/day) that are significantly higher than currently approved in FLONASE® nasal spray (200 mcg/day). In a Pharmacological and Toxicological Review of IND 110,089 dated July 11, 2012, it was stated that "the potential systemic toxicity issues arising from this increased dose appear to be covered under the approved inhalation dose of FLOVENT® at 880 mcg in the HFA product and 1000 mcg in the DPI product. However, local toxicity in the nasal cavities and sinuses may be a concern since previously approved doses for FLONASE® nasal spray (≤ 200 mcg/day) are below the Sponsor's highest proposed dose of (b) (4) mcg/day. Following discussions with the Medical Officer, the potential local toxicities appear to be monitorable in a clinical setting". No additional nonclinical local toxicity studies with the drug product were requested.

There were no nonclinical safety concerns related to excipients, degradants, or impurities. A separate extractables/leachables review will be conducted.

Recommendation: The reviewer recommends approval of this 505(b)(2) NDA from the nonclinical perspective. Labeling should be modified as shown below or Section 1.3.3.

Labeling Review

For this 505(b)(2) NDA, the Sponsor provided a draft label for XHANCE™ based upon the approved product label of the listed drug, FLOVENT® HFA. The product label for FLOVENT® HFA complies with the Pregnancy and Lactation Labeling Rule (PLLR).

The proposed label below does not incorporate any additional changes/modifications provided by the medical officer or Division of Pediatric and Maternal Health (DPMH).

XHANCE™

(b) (4)

XHANCE is a corticosteroid indicated:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4)

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 mcg/m^2

basis [(b) (4)]. 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 on a mcg/m^2 basis [*see* (b) (4) *Data*]. Experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

The estimated risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriages in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

(b) (4)

Data

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 equivalent to the MRHDID (on a mcg/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 0.4 times the MRHDID (on a mcg/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 0.3 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 45 mcg/kg/day). The mouse NOAEL was observed with a dose approximately 0.1 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 15 mcg/kg/day).

In an embryofetal development study with pregnant rats dosed by the inhalation route throughout the period of organogenesis, fluticasone propionate produced decreased fetal body weights and skeletal variations, in the presence of maternal toxicity, at a dose approximately (b) (4) times the MRHDID (on a mcg/m^2 basis with a maternal inhalation dose of 25.7 mcg/kg/day); however, there was no evidence of teratogenicity. The NOAEL was observed with a dose approximately 0.1 times the MRHDID (on a mcg/m^2 basis with a maternal inhalation 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 0.02 times the MRHDID and higher (on a mcg/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 1 fetus at a dose approximately 0.1 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 4 mcg/kg/day). The NOAEL was observed in rabbit fetuses with a dose approximately 0.002 times the MRHDID (on a mcg/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 0.7 times the MRHDID (on a mcg/m^2 basis with 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 child, or the effects on milk production. 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 XHANCE and any potential adverse effects on the breastfed child from XHANCE or from the underlying maternal condition.

Data

(b) (4)

Subcutaneous administration of tritiated fluticasone propionate at a dose in lactating rats approximately 0.1 times the MRHDID for adults (on a mcg/m^2 basis) resulted in measurable levels in milk.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fluticasone propionate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. Fluticasone propionate has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor that is 18 times that of dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results. The clinical significance of these findings is unknown.

The precise mechanism through which fluticasone propionate affects nasal polyps and associated inflammatory symptoms is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (eg, mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. The anti-inflammatory action of corticosteroids contributes to their efficacy. In 7 trials in adults, fluticasone propionate nasal spray decreased nasal mucosal eosinophils in 66% of patients (35% for placebo) and basophils in 39% of patients (28% for placebo). In addition, studies suggest that carbon dioxide, which is present in the exhaled breath delivered into the nose through the device, may influence inflammatory mediator activity and neuropeptide activity, possibly through mechanisms of action that also include removal of nitric oxide, change in pH, or positive pressure. The direct relationship of these findings to long-term symptom relief is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1000 mcg/kg (approximately 7 times the MRHDID for adults on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (approximately equivalent to the MRHDID for adults on a mcg/m^2 basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the in vivo mouse micronucleus test.

Fertility and reproductive performance were unaffected in male and female rats at subcutaneous doses up to 50 mcg/kg (approximately 0.7 times the MRHDID for adults on a mcg/m^2 basis).

Table 2. Dosing calculations for proposed maximum clinical dose of XHANCE™ (Fluticasone propionate) relative to nonclinical carcinogenicity, reproductive, fertility, teratogenicity, and overdosage studies

	XHANCE							
	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m²
Pediatric dose				0	3	0.00	25	0.00
Adult dose	>18	(b) (4)	(b	0.744	60	0.012	37	0.459

					Dose Ratio		Rounded Dose Ratio	
	route	mg/kg/day	factor	mg/m²	Adults	Children		
Carcinogenicity:								
mouse	po	1	3	3	6.5		7	---
rat	po	0.057	6	0.342	0.7		1/1	---
rat	po		6	0	0.0		---	---
rat	po		6	0	0.0		---	---
hamster			4	0	0.0		---	---
extra			20	0	0.0		---	---
Reproduction and Fertility:								
mouse			3	0	0.0		---	---
rat	sc	0.05	6	0.3	0.7		1/2	---
extra			20	0	0.0		---	---
Teratogenicity:								
mouse	sc	0.045	3	0.135	0.3		1/3	---
mouse	sc	0.01	3	0.03	0.1		1/15	---
mouse	sc	0.04	3	0.12	0.3		1/4	---
mouse	sc	0.15	6	0.9	2.0		2	---
rat	sc	0.01	6	0.06	0.1		1/8	---
rat	sc	0.1	6	0.6	1.3		1	---
rat	sc	0.03	6	0.18	0.4		1/3	---
rat	inh	0.026	6	0.156	0.3		1/3	---
rat	inh	0.006	6	0.036	0.1		1/13	---
rabbit	sc	0.0006	12	0.0072	0.0		1/64	---
rabbit	sc	0.00008	12	0.00096	0.0		1/478	---
rabbit	sc	0.004	12	0.048	0.1		1/10	---
Overdosage:			3	0	0.0		---	---
mouse	po	1000	3	3000	6538.8		6500	---
rat	sc	1000	6	6000	13077.6		13000	---
guinea pig			12	0	0.0		---	---
rabbit			12	0	0.0		---	---
monkey			20	0	0.0		---	---
dog			20	0	0.0		---	---
rabbit			12	0	0.0		---	---
extra								

Conversion, Corre	Weight	Factor			Factor			Round to
Human Age	(kg)	(kg/m²)		Species	(kg/m²)		Up to	nearest
(yr)				dog	20		1	1
0	3	25		guinea pig	8		10	5
0.5	7	25		hamster	4		100	10
1	10	25		monkey	12		1000	100
2	12	25		mouse	3		10000	1000
4	16	25		rabbit	12			
6	20	25		rat	6			
12	50	37						
adult	50	37						

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/s/

BRETT R JONES
07/28/2017

ANDREW C GOODWIN
07/28/2017
I concur

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 209022 **Applicant: OptiNose US, Inc.** **Stamp Date: 11/18/2016**

Drug Name: (b) (4) (b) (4) (OPN-375) (Fluticasone propionate) **NDA Type: 505(b)(2)**

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?		X	No new nonclinical studies were requested or conducted to directly support the submission. For the (b) (4) (i.e., fluticasone propionate) exhalation nasal drug delivery product, the applicant is relying upon bioequivalence to the reference listed drugs (RLD), Flonase® (GSK, NDA 020121) and Flovent HFA® (GSK, NDA 021433). The PharmTox information in Module 4 (0001) contains the U.S. product monographs for Flonase® and Flovent HFA®, as well as several literature references. Module 2 (0001) contains written and tabular summaries of available PharmTox information.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?		X	
3	Is the pharmacology/toxicology section legible so that substantive review can begin?		X	
4	Are all required and requested IND studies (in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			Not applicable. No nonclinical studies were requested or submitted.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable. See Comment in #1.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			Not applicable. See Comment in #1.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			Not applicable. See Comment in #1.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable, no studies were requested.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	X		The Sponsor has provided proposed draft labeling for the fluticasone propionate exhalation nasal drug delivery product based upon the labels of the RLDs, Flonase® (labeling approved January, 2015) and Flovent HFA® (labeling approved December, 2014). The proposed label will require updating to comply with the current RLD label(s) now in PLLR format.
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		The PharmTox reviewer will consult with the CMC reviewer regarding any impurity issues.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?	X		This is a 505(b)(2) application (see comment in #1). Bridging for the application was based upon clinical bioequivalence.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the NDA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.
None.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None.

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

/s/

BRETT R JONES
01/04/2017

TIMOTHY W ROBISON
01/04/2017
I concur