CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

CDTL/Summary Review

Date	September 18, 2017
From	Anthony G. Durmowicz, M.D. Lydia Gilbert McClain, M.D.
Subject	Cross-Discipline Team Leader/Summary Review
NDA/BLA # **Supplement#**	NDA 209-022
Applicant	Optinose US, Inc.
Date of Submission	November 18, 2016
PDUFA Goal Date	September 18, 2017
Proprietary Name / **Established (USAN) names**	Xhance nasal spray fluticasone propionate nasal spray
Dosage forms / Strength	Metered dose spray, 93 mcg fluticasone propionate/ (b) (4)
Proposed Indication(s)	For treatment of nasal polyps in patients ≥ 18 years of age
Recommended Action:	*Approval*

1. Introduction

Optinose US, Inc. submitted this 505(b)(2) new drug application for use of fluticasone propionate nasal spray (tradename Xhance) for a proposed indication of treatment of nasal polyps on November 18, 2016, with the GlaxoSmithKline fluticasone propionate inhalation aerosol and nasal spray (Flovent HFA, Flonase) serving as reference products. The application is primarily based on two identical clinical efficacy and safety studies in adult patients with nasal polyps. This review will provide an overview of the application, with a focus on the clinical efficacy and safety studies used to support the proposed indication. The PDUFA date for this application is September 18, 2017.

2. Background

Fluticasone propionate is a well characterized fluorinated corticosteroid that has been available in topical, nasal spray, and inhalational aerosol and dry powder formulations for the treatment of dermatologic, nasal allergy, and respiratory diseases/conditions for the last 25-30 years. It is currently available over the counter as Flonase Allergy Relief nasal spray to treat allergic rhinitis symptoms (hay fever) and as inhalation aerosols and dry powders both alone (Flovent HFA and Diskus) and in combination with beta-adrenergic agonists such as salmeterol (Advair HFA and Diskus) for treatment of asthma and COPD.

Nasal polyps are a chronic condition characterized by eosinophilic inflammatory outgrowths of the nasal mucosa, often occurring bilaterally along the middle and superior meatus. An estimated 4% of the general population develops nasal polyps. The disease primarily affects adults and while not life-threatening, they can cause nasal obstruction, facial pain, hyposmia, and rhinorrhea and have significant impact on quality of life. Treatment of nasal polyps can be difficult. It typically may include both medical and surgical therapy aimed at either complete

elimination of the polyps or sufficient reduction in polyp size to alleviate nasal obstruction and associated symptoms. Medical therapy is largely limited to use of intranasal, and if refractory, systemic corticosteroids. If unsuccessful, surgical treatment is an alternative but recurrence occurs in up to 10% of patients. Currently, there are two corticosteroid-containing nasal spray products approved to treat or prevent recurrence of nasal polyps; mometasone furoate (Nasonex) for the treatment of nasal polyps and beclomethasone dipropionate (Beconase AQ).

Xhance nasal spray was developed under IND# 110,089 which was opened on July 18, 2012. Milestone meetings included Pre-IND and Pre-NDA meetings during which the following discussion/agreements transpired:

- Discussion of the 505(b)(2) pathway, specifically selection of reference drug(s) (RLD) and agreement to reference Flonase nasal spray and/or Flovent HFA inhalation aerosol for clinical pharmacology (e.g. special populations, drug-interactions, HPA axis inhibition, and QT/QTc assessment)
- Long-term safety data of at least 1-year would be needed
- For safety, prospectively evaluate for nasal ulcerations, nasal perforation, and ocular toxicity
- Agreement on the co-primary endpoints, reduction in a nasal polyp grading score and 7-day average nasal congestion / obstruction symptom
- Discussion of CMC, nonclinical and clinical content of submission
- Open-label safety data would be supportive of safety (b) (4)
- Requested submission of a responder analysis for elimination of polyps
- Stated that the Sinonasal Outcome Test-22 (SNOT-22) and patient global assessments (b) (4), but may support efficacy

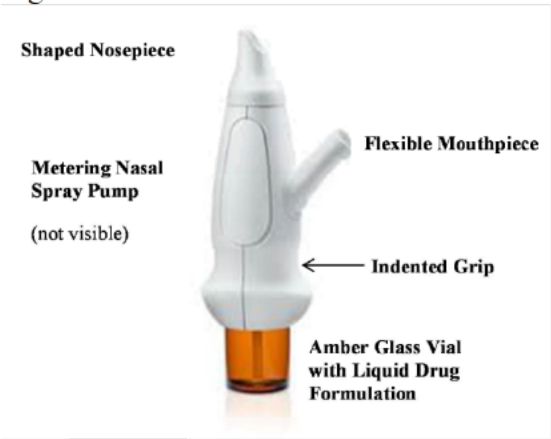
A Pediatric Study Plan was also agreed upon in November 2015, which included a (b) (4) waiver for children <6 years of age and deferral in children and adolescents 6 to 17 years of age. The program for patients 6-17 years of age (b) (4)

3. CMC/Device

The drug substance fluticasone propionate is a well-known glucocorticoid compound that has been previously been used as the active ingredient for several marketed nasal and orally administered spray and aerosol products for use in patients with allergic rhinitis, asthma, and COPD. It is manufactured by (b) (4)

The drug product Xhance (developmental name OPN-375) is a nonsterile aqueous, milky white suspension of fluticasone propionate delivered by a unique non-pressurized, multi-dose nasal spray device described as a "Breath Powdered Exhalation Delivery System" (in which the patient blows into the mouthpiece while actuating the nasal spray device) that is proposed to facilitate drug delivery to the target regions of the nasal mucosa (Figure 1). Compendial excipients include polysorbate 80, microcrystalline cellulose, carboxymethylcellulose sodium, EDTA, benzalkonium chloride, dextrose, and (b) (4) and (b) (4) .

Figure 1. Assembled Xhance Device



Each (b) (4) spray delivers an actual dose of 93-mcg fluticasone propionate ((b) (4)). After priming, each OPN-375 device delivers 120 sprays.

All DMFs, manufacturing and testing facilities associated with this application have been deemed acceptable. In addition, CDRH inspections of the drug product manufacturer (Contract Pharmaceuticals Limited, Canada) and sub assembly manufacturer (Ximedica, LLC) were performed and classified as NAI.

The stability data support a 24 month expiry period.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were conducted or required to support the current NDA. Optinose has referenced Flonase nasal spray to support the local toxicology for fluticasone administered intranasally. A toxicological assessment of extractables studies conducted with the container-closure system raised no concerns.

5. Clinical Pharmacology/Biopharmaceutics

The general clinical pharmacology and pharmacodynamic considerations for the Xhance program were referenced from the approved Flovent HFA inhalation aerosol and Flonase nasal spray fluticasone propionate containing products. To support the reference, Optinose conducted an open label, single dose clinical pharmacology study (Study 1102) to compare the relative bioavailability of the proposed OPN-375 (fluticasone propionate) nasal spray product to that for both Flovent HFA inhalation aerosol and Flovent nasal spray.

Study 1102 was a 2-part, single-dose randomized, open-label, study conducted under fasting conditions. Part 1 had a 3-way crossover, 3-treatment, 3-sequence design. In it, 90 adult healthy volunteers were randomized (1:1:1) to receive single doses of 186 mcg OPN-375, 372 mcg OPN-375 or 400 mcg Flonase. Part 2 had a 2-way crossover, 2-treatment, 2-sequence design in which 30 healthy volunteers were randomized (1:1) to receive single doses of either 372 mcg OPN-375 or 440 mcg Flovent HFA. Blood was collected for serial PK samples pre- and post-dose for up to 24 hours (Part 1) and 36 hours (Part 2).

Results of the pharmacokinetic analyses demonstrated that the systemic exposure of OPN-375 at the highest dose was below the prespecified bioequivalence margin for Flovent HFA 440 mcg (but generally higher than that for Flonase 400 mcg), establishing Flovent HFA as the appropriate reference listed drug for systemic safety, including HPA axis effect (Table 1).

Table 1. Summary bioavailability PK data for in Study 1102

PK parameter	% GLSM ratio*	90% CI
OPN-375 2x93-mcg/Flonase® 400 mcg		
C_{max} (pg/mL)	137.1	126.8, 148.1
AUC_t (pg h/mL)	101.8	93.3, 111.2
AUC_∞ (pg h/mL)	94.4	83.4, 106.8
OPN-375 4x93-mcg/Flonase® 400 mcg		
C_{max} (pg/mL)	201.7	186.7, 218.0
AUC_t (pg h/mL)	159.8	146.4, 174.4
AUC_∞ (pg h/mL)	144.6	128.1, 163.3
OPN-375 4x93-mcg/Flovent® HFA 440 mcg		
C_{max} (pg/mL)	63.2	50.6, 78.8
AUC_t (pg h/mL)	49.2	40.0, 60.6
AUC_∞ (pg h/mL)	49.9	41.0, 60.7
*GLSM = geometric least squares mean based on log-transformed parameters.		

6. Clinical Microbiology

As a nasally administered product, Xhance nasal spray is not required to be sterile. Manufacturing specifications regarding possible microbiological contamination are adequate. Benzalkonium chloride and EDTA are present in the drug product to (b) (4)

7. Clinical/Statistical- Efficacy

Overview of the Clinical Program

The core clinical program submitted by Optinose to support this application included two identical efficacy and safety trials in patients with bilateral nasal polyps and two open label safety trials of up to one year duration in which patients with chronic sinusitis with or without nasal polyps received the highest proposed dose of 372 mcg twice daily. A formal dose-ranging study was not performed. This was acceptable as the efficacy and safety trials included three active drug treatment groups and, as such, also served as dose selection studies. The basic design characteristics of relevant clinical studies submitted to support the application are outlined below in Table 2. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions.

Table 2. Relevant Clinical Studies for the Xhance Program

Study Year Begun	**Study type**	**Study Duration**	**Patient Age, yrs**	**Treatment Groups***	**N (ITT)**	**Co-Primary efficacy variables**	**Countries**
OPN-3101 2013	Efficacy and Safety	16 weeks	≥ 18 yrs	OPN-375 93 mcg bid OPN-375 186 mcg bid BDP HFA 372 mcg bid Placebo	81 80 80 82	Reduction in nasal polyp grade Reduction in nasal congestion	USA, Canada, Czech Republic, UK, Ukraine, South Africa
OPN-3102 2013	Efficacy and Safety	16 weeks	≥ 18 yrs	OPN-375 93 mcg bid OPN-375 186 mcg bid BDP HFA 372 mcg bid Placebo	81 80 82 80	Reduction in nasal polyp grade Reduction in nasal congestion	USA, Poland, Romania, Ukraine, South Africa
OPN-3203 2013	Open label safety	12 months	≥ 18 yrs	OPN-375 372 mcg bid	223	Safety	USA
OPN-3204 2013	Open label safety	12 weeks	≥ 18 yrs	OPN-375 372 mcg bid	705	Safety	USA

* OPN-375 = fluticasone nasal spray administered in each nostril (93 mcg/actuation)

Design and Conduct of the Efficacy and Safety Studies

The efficacy and safety studies (Studies 3101 and 3102) were identical 16-week, randomized, double-blind, placebo-controlled, parallel group, and multicenter studies that evaluated the efficacy and safety of intranasal administration of three doses of OPN-375 (93, 186, and 372 mcg fluticasone propionate twice daily) using a novel nasal spray device in patients 18 years of age and older with bilateral nasal polyposis and nasal congestion.

The studies consisted of a blinded placebo run-in phase of 7 to 14 days duration, a 16-week double-blind treatment phase, and an 8-week open-label extension during which all subjects received the high dose of 372 mcg twice daily. At the end of the run-in phase, eligible subjects entered into the double-blind treatment phase. Subjects were randomized in a 1:1:1:1 ratio to receive placebo, 93 mcg, 186 mcg, or 372 mcg of OPN-375 twice daily.

Eligible patients had grade 1-3 bilateral nasal polyps in each nostril and at least moderate symptoms of nasal congestion. Patients with near complete nasal obstruction, those with nasal septal perforations, ≥ 5 sinonasal surgeries, purulent nasal infection, structural oral abnormalities, and a dx of cystic fibrosis, ciliary dyskinesia, or Churg-Strauss were excluded. Subjects were permitted continued use of saline nasal sprays and saline lavage if these were already being used before study entry. Before entry into this study, subjects were required to stop the use of all medications that could potentially alleviate symptoms of nasal congestion (such as intranasal steroids, oral antihistamines). After the nasal congestion endpoint was assessed at Week 4, patients were permitted to use non-sedating antihistamines as rescue on an as-needed basis for the remainder of the study.

The two co-primary efficacy variables were reduction of nasal congestion/obstruction symptoms at Week 4 and reduction in the nasal polyp grade at Week 16. The reduction of nasal congestion/obstruction symptoms at Week 4 was defined as the change from baseline (the average score obtained from the values recorded during the last 7 days in the run-in period

immediately prior to Day 1 in instantaneous morning diary symptom scores to the average score over the 7 days prior to the Week 4 visit. Symptoms graded on a scale of 0 (no symptoms to 3 (severe symptoms) included nasal congestion/obstruction, rhinorrhea, facial pain or pressure symptoms, and sense of smell.

The reduction in nasal polyp grade at Week 16 was defined as the change from the screening baseline in the total polyp grade (sum of scores from both nasal cavities) at the Week 16 assessment. Polyp grade of each nasal cavity was determined on a four-point polyp grading scale (0 – no polyps, 1- mild polyposis, 2 - moderate polyposis, 3 - severe polyposis) using nasoendoscopy at screening, Week 4, Week 8, Week 12, Week 16, and Week 24 visits.

Reduction of nasal congestion/obstruction symptoms endpoint was analyzed using an analysis of covariance (ANCOVA) model with the baseline nasal symptom score as a covariate, treatment and country as factors. The reduction in total polyp grade endpoint was analyzed using a mixed effect model for repeated measures that included terms for baseline score, treatment, country, visit, and the treatment-by-visit interaction. The efficacy analyses were carried out using the full analysis set, defined as all randomized subjects who received at least one dose of double-blind study drug and had baseline assessments for the two co-primary endpoints. A sequential testing procedure was implemented to control the study-wise Type I error at level 0.05. The highest dose, 372 mcg, was tested against placebo first, followed by the 186 mcg dose, and then the 93 mcg dose. The test could proceed to the next lower dose only if the higher dose was better than placebo in both co-primary endpoints with statistical significance at level 0.05.

Key secondary endpoints included the mean change in the Sinonasal Outcome Test - 22 (SNOT-22) total score at Week 16 and the mean change in the Sleep Disturbance subscale score of the MOS Sleep-R at Week 16. Statistical multiplicity between the two key secondary variables was controlled using a stepdown method analogous to that utilized for the primary outcome variables.

Disposition and Demographics
A total of 323 subjects were randomized in each of Studies 3101 and 3102 with over 90% completing the double-blind portions of each study. The demographic and baseline characteristics were comparable across treatment groups for both studies. The large majority of patients enrolled were White, 88% and 94% for Studies 3101 and 3102, respectively. For Study 3101, 50% of the patients were male with 44% of the patients were enrolled from US sites. For Study 3102, 58% of patients were male with 41% enrolled from US sites.

Efficacy Findings and Conclusions
The submitted studies support the efficacy of Xhance nasal spray at doses of 186 and 372 mcg (one or two, 93 mcg actuations in each nostril) administered twice daily for the treatment of nasal polyps.

In Study 3101, the treatment effects of the three active doses of OPN-375 resulted in statistically significant improvements in both nasal symptom scores and nasal polyp grade. The treatment effects for both of these co-primary endpoints were numerically larger for the

two higher doses, 186 mcg and 371 mcg twice daily, were numerically larger compared to the lower 93 mcg twice daily dose (Tables 3 and 4).

Similarly, the same three active doses of OPN-375 used in Study 3102 were superior to placebo for both co-primary endpoints (Tables 2 and 3). In this study, for the co-primary endpoints, the higher doses did not convincingly separate from the lower 93 mcg twice daily dose but when the endpoint "change in polyp grade over time" was assessed, the 186 mcg and 372 mcg doses twice daily appeared to perform better.

Results were consistent across gender and geographic region. There were insufficient non-White patients and those > 65 years to be able to identify potential differences in response to treatments.

Table 3. Reduction of Nasal Congestion/Obstruction Symptoms at Week 4 (Trials 3101 and 3102)

	Placebo	**OPN-375**		
		93-mcg BID	**186-mcg BID**	**372-mcg BID**
Trial 3101	N=82	N=81	N=80	N=79
Baseline mean (SD)	2.3 (0.41)	2.2 (0.44)	2.2 (0.42)	2.3 (0.44)
Change baseline to Week 4				
LS mean	-0.24	-0.49	-0.54	-0.62
Difference (active-placebo)		-0.25	-0.30	-0.38
95% CI		(-0.43, -0.06)	(-0.48, -0.11)	(-0.57, -0.19)
p-value versus placebo		0.01	0.002	<0.001
Trial 3102	N=79	N=80	N=80	N=82
Baseline mean (SD)	2.3 (0.43)	2.2 (0.41)	2.2 (0.37)	2.2 (0.42)
Change baseline to Week 4				
LS Mean	-0.24	-0.59	-0.68	-0.62
Difference (active-placebo)		-0.36	-0.45	-0.38
95% CI		(-0.56, -0.16)	(-0.65, -0.25)	(-0.58, -0.18)
p-value versus placebo		<0.001	<0.001	<0.001

LS= least square; CI= confidence interval; SD= standard deviation. Score of 2 indicates moderate intensity.

Table 4. Reduction in Total Nasal Polyp Grade at Week 16 (Trials 3101 and 3012)

	Placebo	OPN-375		
		93-mcg BID	186-mcg BID	372-mcg BID
Trial 3101	N=82	N=81	N=80	N=79
Baseline mean (SD)	3.8 (0.94)	3.6 (1.07)	3.9 (1.08)	3.7 (0.94)
Change from baseline to Week 16				
LS mean	-0.45	-0.96	-1.03	-1.06
Difference (active-placebo)		-0.51	-0.59	-0.62
95% CI		(-0.86, -0.16)	(-0.93, -0.24)	(-0.96, -0.27)
p-value versus placebo		0.004	< 0.001	<0.001
Trial 3102	N=79	N=80	N=80	N=82
Baseline mean (SD)	3.8 (1.08)	3.6 (0.98)	3.9 (1.05)	3.9 (1.00)
Change from baseline to Week 16				
LS Mean	-0.61	-1.31	-1.22	-1.41
Difference (active-placebo)		-0.70	-0.60	-0.80
95% CI		(-0.99, -0.41)	(-0.89, -0.31)	(-1.08, -0.51)
p-value versus placebo		<0.001	<0.001	<0.001

LS= least square; CI= confidence interval; SD= standard deviation; N = number of subjects in each treatment arm.

Analyses of other efficacy endpoints such as SNOT-22, sleep disturbance, and use of rescue medication was also supportive of efficacy.

Onset of Action
Onset of action, defined as the time at which the treatment effect of OPN-375 on daily instantaneous AM congestion scores started to achieve statistical significance in comparison to placebo and was maintained thereafter, was evaluated in both the Studies 3101 and 3102. For both trials, the consistent treatment effect was generally observed during the second week of treatment (approximately day 10-11). A statement regarding onset of action will be added to the product labeling.

8. Safety

Safety database
The safety assessment of Xhance nasal spray is based primarily on the two 16-week randomized, placebo-controlled trials (Studies 3101 and 3102) and additional open-label safety data for up to 12 months of exposure to the highest proposed dose of 372 mcg twice daily (Table 2).

In these studies over 1,500 patients received Xhance at doses ranging from 93 to 372 mcg twice daily with approximately 147 patients receiving the highest indicated dose of 372 mcg twice daily for up to one year. For the two phase 3 studies, a total of 643 adult subjects with bilateral nasal polyps and associated moderate or severe nasal congestion were enrolled of which 161 received 93 mcg twice daily, 160 received 186 mcg twice daily, 161 received 372 mcg twice daily and 161 received placebo. Of these 46.0% were female, 91% White, 6% Black, and 1% Asian. Seven percent were 65 years of age or older.

Fluticasone propionate is a well-characterized corticosteroid that is the active drug substance for several nasal and inhaled administered products used to treat SAR/PAR (non-prescription), asthma, and COPD. Considering this wealth of clinical experience, the size of the database is adequate.

Safety Findings and Conclusion
The submitted data support the safety of Xhance nasal spray in patients 18 years of age and older. No new safety signals were identified that differ from both the known safety profile of fluticasone propionate and class effects of other intranasal corticosteroids. The most common adverse events observed in the active treatment arms were epistaxis, nasopharyngitis, and nasal septal ulceration, with epistaxis demonstrating a small dose-response. Other local adverse events of interest such as posterior subcapsular cataracts, elevated intraocular pressure, and nasal septal perforation, were infrequently identified in both subjects exposed to fluticasone propionate and placebo and were without a clear dose-response.

There were no deaths in the clinical program.

Serious adverse events were uncommon with a total of 3 in patients on active treatment; worsening polyps (93 mcg dose), and positional vertigo and menorrhagia (372 mcg dose). These were not likely to be related to a nasally-administered corticosteroid such as fluticasone nor did they suggest a new safety signal.

Study discontinuations due to adverse events were relatively uncommon in the 16-week double-blind, placebo-controlled trials and similar in number between patients in active treatment groups and the placebo group, approximately 2% and 4%, respectively. In the open label safety studies up to one year in duration, 4.8% of patients discontinued due to an adverse event with epistaxis being the most common reported event (1.2%).

Local adverse reactions such as epistaxis, nasal ulcerations, and nasal septal perforations are known class effects of nasally administered corticosteroid products. Epistaxis occurred relatively frequently, in about 20% of patients on active treatment compared to 6% of those receiving placebo, and there was a small dose response. The overall incidence of epistaxis was higher than reported with other intranasal corticosteroids, but likely reflects the definition of epistaxis used, which included evidence of past bleeding on nasoendoscopy exam as well as spontaneous reports by the patient. Looking just at patient-reported epistaxis, the incidence was less, approximately 10-12% in patients receiving the indicated doses of 186 mcg and 372 mcg. This is still somewhat higher than for that of other nasal products approved for SAR/PAR but is consistent with that reported for other nasal steroid products used to treat nasal polyps and not surprising given the chronically inflamed nature of nasal polyp mucosa.

Nasal septal and mucosal ulcerations also occurred more in patients on active treatment, about 7% and 3%, respectively for patients receiving the 186 mcg and 372 mcg doses compared to about 2% for those receiving placebo.

There were a total of 4 nasal septal perforations observed in the Xhance clinical development program. A nasal septal perforation was reported in 1 patient who received the 186 mcg dose

compared with none treated with placebo. The patient had a prior history of nasal/sinus surgery. Three patients treated with the 372 mcg dose twice daily in uncontrolled, open-label trials of 3 to 12 months duration also developed nasal septal perforations.

Detailed ophthalmologic data were collected patients enrolled in the clinical program to assess for corticosteroid-related ocular effects including lens opacification (cataracts), and intra-ocular pressure (IOP). For intraocular pressure, a value ≥21 mmHg was considered as abnormal eye pressure. The evaluation of lens opacification/cataracts used the Lens Opacities Classification System Version III (LOCS III), a standard method of grading lens opacities.

In the placebo-controlled trials, there were no meaningful differences in mean IOP at the conclusion of the 16-week treatment period for any treatment arm. The highest IOP in the trials was 24 mmHg, and occurred in both the placebo and the low dose 93-mcg twice daily arms. Open-label data on IOP were consistent with that from the placebo-controlled trials.

Eight patients developed treatment emergent cataracts during the placebo-controlled 16-week trials of which 3 were noted to be posterior subcapsular in nature, those typically associated with corticosteroid use. These occurred in patients receiving either the 186 mcg or 372 mcg twice daily doses. While the formation of posterior subcapsular cataracts is suggestive of a corticosteroid-related effect, cataracts are not expected in a study of short (16-week) duration. As such, confounding factors such as prior use of intranasal or systemic corticosteroids may contribute to this finding. In the longer, one-year open-label studies, 11 patients were noted to develop treatment emergent cataracts, however none were posterior subcapsular in nature.

HPA axis effect is typically assessed in clinical programs for corticosteroid products. For the Xhance program, the Optinose is relying on the data on HPA axis effect used for the Flovent HFA inhalation aerosol reference product. This is appropriate as the systemic exposure of fluticasone propionate was lower for the nasally administered doses used in the Xhance program than those in subjects who received the labeled dose of 440 mcg of fluticasone propionate as Flovent HFA (see Clinical Pharmacology section above). (b) (4)

[redacted]

9. Advisory Committee Meeting

An advisory committee was not convened for this application. Fluticasone propionate is a well characterized corticosteroid and has been used for many years in nasally and orally administered products to treat allergic rhinitis and asthma. In addition, the efficacy and safety findings seen in the clinical program were robust in their support of efficacy. As such, there were no issues that warrant discussion at an advisory committee meeting.

10. Pediatrics

The phase 3 studies included for this nasal polyp program included adults only. The Applicant submitted a pediatric plan which was agreed to in November 2015, which included a (b) (4)

waiver for children <6 years of age and deferral in children and adolescents 6 to 17 years of age. The program for (b) (4) the PREA PMR for the program will consist of a single safety and efficacy study in pediatric patients with nasal polyps.

(b) (4)

11. Other Relevant Regulatory Issues

- Financial Disclosure: With respect to the 2 Phase 3 trials, Studies 3101 and 3102, the Applicant certified that it did not enter into financial arrangements with any investigator whereby the value of compensation could be affected by the outcome of the study as defined in 21 CFR 54.2(a), that no investigator received significant payments as defined in 21 CFR 54.2(f), that none of the investigators disclosed a proprietary interest in the product, or possessed a significant equity interest in the Applicant as defined in 21 CFR 54.2(b).
- DSI audits: Clinical site inspections were conducted for two foreign clinical sites primarily because of high enrollment. An Applicant level inspection of Optinose US Inc. was also conducted because both pivotal trials involved a large number of sites with small subject enrollment at each site, and because the Applicant is a small, relatively unknown entity with whom we have no significant experience. Inspections showed no substantial irregularities and resulted in either No Action Indicated (both clinical sites) or Voluntary Action Indicated (Applicant). All studies were performed in accordance with acceptable ethical standards.

12. Labeling

- Proprietary Name: The name Xhance nasal spray was judged acceptable
- Physician Labeling: The label was reviewed by various disciplines within DPARP, the Office of Medical Policy Programs (OMPP), DRISK, DMEPA, and by OPDP. Various changes to different sections of the label were made to reflect the data accurately and better communicate the findings to healthcare providers. The patient Instructions for Use labeling was extensively revised to add additional art work to help patients comprehend how to use the novel nasal spray delivery device. Final labeling has been agreed upon.

13. Recommendations/Risk Benefit Assessment

- Regulatory Action

The regulatory action is approval of Xhance nasal spray for the treatment of nasal polyps in patients 18 years of age and older.

- Risk Benefit Assessment

The overall risk and benefit assessment of Xhance nasal spray supports its approval for the treatment of nasal polyps in patients 18 years of age and older. Efficacy was confirmed in two identical phase 3 studies in which patients with bilateral nasal polyps treated with Xhance demonstrated significant improvements both nasal polyp grade and reduction in nasal symptoms. Safety findings were consistent with those observed for other nasally administered corticosteroid products and included local side effects such as epistaxis, nasal ulcerations, and rare nasal perforations.

- Postmarketing Risk Management Activities

None other than standard pharmacovigilance.

- Postmarketing Study Commitments

Optinose has agreed to the following PREA mandated study and timelines.

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 OPN-375 (tradename Xhance) in improving nasal polyp grade and symptoms (nasal congestion/obstruction, sense of smell, rhinorrhea and facial pain or pressure).

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

- Comments to Applicant

None

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