

CENTENE PHARMACY AND THERAPEUTICS  
DRUG REVIEW  
1Q18 January – February

**BRAND NAME**

Xhance™

**GENERIC NAME**

Fluticasone propionate

**MANUFACTURER**

Optinose

**DATE OF APPROVAL**

September 18<sup>th</sup>, 2017

**PRODUCT LAUNCH DATE<sup>1</sup>**

Second quarter of 2018

**REVIEW TYPE**

Review type 1 (RT1): New Drug Review  
*Full review of new chemical or biologic agents*

Review type 2 (RT2): New Indication Review  
*Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use*

Review type 3 (RT3): Expedited CMS Protected Class Drug Review  
*Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)*

Review type 5 (RT5): Abbreviated Review for Intravenous Chemotherapy Agents  
*Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit*

**FDA APPROVED INDICATION(S)<sup>2</sup>**

Treatment of nasal polyps in patients 18 years of age or older.

**OFF LABEL USES**

Not applicable

**CLINICAL EFFICACY**

Background<sup>3</sup>

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Nasal polyps are benign lesions of mucosa in the nasal sinus or cavity that consist of around 4% of the general population who are predominantly adults. Nasal polyps may be associated with allergy, asthma, aspirin sensitivity, cystic fibrosis, and allergic fungal sinusitis.

Therapy may include observation, medical or surgical treatments. The aim of treatment is to improve sinus drainage, restore olfaction and taste. Patients are typically treated in the primary care setting prior to surgery with an otolaryngologist.

The recommended treatment is to start with a topical nasal steroid in addition to treating the underlying cause or allergy.

Sotores D., et al. A randomized, double-blind of NAVIGATE 1 <sup>4</sup>	
<b>Study Design</b>	<p>A phase 3, randomized, double-blind, placebo-controlled study</p> <p>Patient eligibility criteria:</p> <ul style="list-style-type: none"> <li>Eligible patients were at least 18 years of age and had chronic rhinosinusitis with nasal polyps (CRSwNP), with a polyp grade of 1 to 3 in each of the nasal cavities and moderate-severe symptoms of nasal congestion/obstruction at entry.</li> </ul>
<b>N</b>	323
<b>Drug Regimen</b>	Xhance of 93 µg (n=81), 186 µg (n=80), 372 µg (n=80), and placebo (n=82) were given twice daily for 4 and 16 weeks.
<b>Primary Outcome(s)</b>	<p>Co-primary endpoints:</p> <ul style="list-style-type: none"> <li>Reduction of nasal congestion and obstruction symptoms after week 4 from the “Average Diary Score, 7-day, Instantaneous AM”.</li> <li>Reduction in total polyp grade at week 16 from the nasal polyp grading score (0-3 per nostril, summed) via nasoendoscopy.</li> </ul>
<b>Secondary Outcome(s)</b>	<p>Key secondary endpoints (controlled for multiplicity):</p> <ul style="list-style-type: none"> <li>Sino-nasal outcome test (SNOT-22) and Medical outcomes sleep study scale – revised (MOS-Sleep-R).</li> </ul> <p>Other secondary endpoints:</p> <ul style="list-style-type: none"> <li>Patient-reported nasal symptoms assessment.</li> <li>Objective endoscopic assessments of polyp grades.</li> <li>Quality of life (QoL) assessments</li> <li>Surgical intervention assessment.</li> <li>Medication evaluation questionnaire.</li> </ul>
<b>Results</b>	<p>Co-primary endpoints:</p> <ul style="list-style-type: none"> <li>At week 4 (p&lt;0.01) least squares (LS) mean change in congestion:             <ul style="list-style-type: none"> <li>Placebo (-0.24), 93 µg (-0.49), 186 µg (-0.54), 372 µg (-0.62)</li> </ul> </li> <li>At week 16 (p&lt;0.01) LS mean change in summed polyp grade:             <ul style="list-style-type: none"> <li>Placebo (-0.45), 93 µg (-0.96), 186 µg (-1.03), 372 µg (-1.06)</li> </ul> </li> <li>Mean change in core symptoms score at week 4 (p-values):</li> </ul>

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	Congestion/ obstruction	Rhinorrhea	Facial pain or pressure	Sense of smell
Placebo	-0.26	-0.23	-0.18	-0.04
93µg	-0.51 (<0.01)	-0.48 (<0.01)	-0.35 (N/A)	-0.23 (<0.05)
186µg	-0.55 (<0.01)	-0.55 (<0.01)	-0.43 (<0.01)	-0.21 (N/A)
372µg	-0.64 (<0.001)	-0.55 (<0.01)	-0.39 (<0.01)	-0.33 (<0.01)
	<p>Key secondary endpoints (controlled for multiplicity):</p> <ul style="list-style-type: none"> <li>At week 16, SNOT-22 improvement was substantial in all EDS-FLU and superiorly statistically significant compared to placebo (p&lt;0.005).</li> <li>Patient-reported nasal symptoms assessment showed almost 2x proportional change in very much/much improvement compared to placebo (p&lt;0.005).</li> <li>At week 16, percent change of &gt;1 point improvement in polyp grade [p-value]:               <ul style="list-style-type: none"> <li>Placebo (41%), 93 µg (56%) [N/A], 186 µg (66%) [&lt;0.01], 372 µg (72%) [&lt;0.001]</li> </ul> </li> <li>At week 4, QoL was statistically significant in all EDS-FLU groups versus placebo.</li> <li>At week 16, percent change in surgical eligibility [p-value N/A]:               <ul style="list-style-type: none"> <li>Placebo (-49%), 93 µg (-62%), 186 µg (-52%), 372 µg (-60%)</li> </ul> </li> </ul>			
<b># Withdrew due to Lack of Efficacy</b>	A total of 14.6% in the placebo group, 93 µg (7.4%), 186 µg (11.3%), 372 µg (5.0%) in the Xhance group withdrew due to lack of efficacy.			
<b># Withdrew due to Adverse Effects</b>	Not reported			

<b>Leopold D., et al. Randomized, Double-blind of NAVIAGE II<sup>5</sup></b>	
<b>Study Design</b>	<p>A phase 3, randomized, double-blind, placebo-controlled study</p> <p>Patient eligibility criteria:</p> <ul style="list-style-type: none"> <li>Eligible patients were at least 18 years of age with CRSwNP with a polyp grade of 1 to 3 in each of the nasal cavities and moderate-severe symptoms of nasal congestion/obstruction</li> </ul>
<b>N</b>	323
<b>Drug Regimen</b>	Xhance of 93 µg (n=81), 186 µg (n=80), 372 µg (n=82), and placebo (n=80) were given twice daily for 4 and 16 weeks.
<b>Primary Outcome(s)</b>	<p>Co-primary endpoints:</p> <ul style="list-style-type: none"> <li>Reduction of nasal congestion and obstruction symptoms after week 4 from the “7-day instantaneous AM average diary score”.</li> </ul>

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	<ul style="list-style-type: none"> <li>Reduction in total polyp grade at week 16 from the nasal polyp grading score (0-3 per nostril, summed) via nasoendoscopy.</li> </ul>																									
<b>Secondary Outcome(s)</b>	<ul style="list-style-type: none"> <li>Patient-reported nasal symptom assessments.</li> <li>Objective endoscopic assessments of polyp grades.</li> <li>QoL assessments.</li> <li>Surgical intervention assessment.</li> <li>Medication evaluation questionnaire.</li> </ul>																									
<b>Results</b>	<p>Co-primary endpoints:</p> <ul style="list-style-type: none"> <li>At week 4 (p&lt;0.001) least squares (LS) mean change in congestion:           <ul style="list-style-type: none"> <li>Placebo (-0.24), 93 µg (-0.59), 186 µg (-0.68), 372 µg (-0.62)</li> </ul> </li> <li>At week 16 (p&lt;0.01) LS mean change in summed polyp grade:           <ul style="list-style-type: none"> <li>Placebo (-0.61), 93 µg (-1.31), 186 µg (-1.22), 372 µg (-1.41)</li> </ul> </li> <li>Mean change in core symptoms score at week 4 (p&lt;0.05):</li> </ul> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th></th> <th style="text-align: center;">Congestion/ obstruction</th> <th style="text-align: center;">Rhinorrhea</th> <th style="text-align: center;">Facial pain or pressure</th> <th style="text-align: center;">Sense of smell</th> </tr> </thead> <tbody> <tr> <td>Placebo</td> <td style="text-align: center;">-0.23</td> <td style="text-align: center;">-0.17</td> <td style="text-align: center;">-0.16</td> <td style="text-align: center;">-0.06</td> </tr> <tr> <td>93 µg</td> <td style="text-align: center;">-0.60</td> <td style="text-align: center;">-0.58</td> <td style="text-align: center;">-0.40</td> <td style="text-align: center;">-0.28</td> </tr> <tr> <td>186 µg</td> <td style="text-align: center;">-0.71</td> <td style="text-align: center;">-0.62</td> <td style="text-align: center;">-0.51</td> <td style="text-align: center;">-0.22</td> </tr> <tr> <td>372 µg</td> <td style="text-align: center;">-0.63</td> <td style="text-align: center;">-0.58</td> <td style="text-align: center;">-0.47</td> <td style="text-align: center;">-0.27</td> </tr> </tbody> </table> <p>Secondary endpoints:</p> <ul style="list-style-type: none"> <li>At week 16, SNOT-22 improvement was substantial in all EDS-FLU and superiorly statistically significant compared to placebo (p&lt;0.001).</li> <li>Two-thirds of patient-reported nasal symptoms assessment showed very much/much improvement compared to 29% placebo (p&lt;0.001).</li> <li>Proportion of patients with polyps eliminated in at least one nostril [p&lt;0.05] all groups +372 µg EDS-FLU at week 24:           <ul style="list-style-type: none"> <li>Placebo (8.7%), 93 µg (24.7%), 186 µg (24.6%), 372 µg (28.2%)</li> </ul> </li> <li>At week 4, QoL was statistically significant in all EDS-FLU groups versus placebo.</li> <li>At week 16 percent change in surgical eligibility [p-value N/A]:           <ul style="list-style-type: none"> <li>Placebo (-49%), 93 µg (-68%), 186 µg (-69%), 372 µg (-62%)</li> </ul> </li> </ul>		Congestion/ obstruction	Rhinorrhea	Facial pain or pressure	Sense of smell	Placebo	-0.23	-0.17	-0.16	-0.06	93 µg	-0.60	-0.58	-0.40	-0.28	186 µg	-0.71	-0.62	-0.51	-0.22	372 µg	-0.63	-0.58	-0.47	-0.27
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372 µg	-0.63	-0.58	-0.47	-0.27																						
<b># Withdrew due to Lack of Efficacy</b>	A total of 12.5% in the placebo group, 93 µg (3.7%), 186 µg (5.0%), and 372 µg (0%) in the Xhance group withdrew due to lack of efficacy.																									
<b># Withdrew due to Adverse Effects</b>	Not reported																									

**CONTRAINDICATIONS**

Xhance is contraindicated in patients with hypersensitivity to any of the ingredients.

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**BLACK BOX WARNINGS**

Not applicable

**DRUG INTERACTIONS**

Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole): Use not recommended. May increase risk of systemic corticosteroid effects.

**ADVERSE REACTIONS**

The most common adverse reactions (incidence 3%) are epistaxis, nasal septal ulceration, nasopharyngitis, nasal mucosal erythema, nasal mucosal ulcerations, nasal congestion, acute sinusitis, nasal septal erythema, headache, and pharyngitis.

**DOSAGE AND ADMINISTRATION**

- For intranasal use only. Xhance is delivered into the nose by actuating the pump spray into one nostril while simultaneously blowing into the mouthpiece of the device.
- Recommended adult dosage: One spray per nostril twice daily (total daily dose of 372 mcg). Two sprays per nostril twice daily may also be effective in some patients (total daily dose of 744 mcg).

**PRODUCT AVAILABILITY**

Nasal spray: 93 mcg of fluticasone propionate in each 106-mg with 120 metered sprays per device.

**THERAPEUTIC ALTERNATIVES<sup>6,7,8</sup>**

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)	COMMENTS
mometasone furoate (Nasonex <sup>®</sup> )	2 sprays/nostril (50mcg/spray) twice daily (400 mcg/day)	
fluticasone propionate (Flonase <sup>®</sup> )	200mcg (50mcg/spray) intranasally once or twice daily OR 400 mcg intranasally once or twice daily.	Off-labeled use.
budesonide (Rhinocort <sup>®</sup> )	128 mcg (32mcg/spray) intranasally once daily OR 400 mcg / day intranasally in 2 divided doses	Off-labeled use.

*Therapeutic alternatives are listed as Brand name<sup>®</sup> (generic) when the drug is available by brand name only and generic (Brand name<sup>®</sup>) when the drug is available by both brand and generic.*

Utilization Management Recommendation
There is not significant potential for inappropriate use.
Product Comparison

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- Equal therapeutic outcomes are anticipated for Xhance, mometasone furoate, fluticasone propionate, and budesonide nasal sprays; therefore, it would be clinically appropriate to provide equal access to all or to require a trial of one before the others.
- Although not clinically required, it would be appropriate to limit the quantity of Xhance to 2 devices per 30 days.

## REFERENCES

<sup>1</sup> Optinose®. Optinose® announces FDA approval of Xhance nasal spray for the treatment of nasal polyps. Sep 2017; Available at: <http://www.optinose.com/press-releases/optinose-announces-fda-approval-xhance-fluticasone-propionate-nasal-spray-treatment-nasal-polyps>. Accessed October 9, 2017.

<sup>2</sup> Xhance [Prescribing Information]. Yardley, PA; Optinose®: September 2017. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/209022s0001b1.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209022s0001b1.pdf). Accessed October 9, 2017.

<sup>3</sup> Newton JR, Ah-see KW. A review of nasal polyposis. Ther Clin Risk Manag. 2008;4(2):507-12. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2504067/>. Accessed October 9, 2017

<sup>4</sup> Soteres D., Messina J., Carothers J., et al. A randomized, double-blind of an Exhalation Delivery System with fluticasone (EDS-FLU) for treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) (NAVIGATE I). Journal of Allergy and Clinical Immunology, Volume 139, Issue 2, AB66. Feb 2017 Available at: [http://www.optinose.com/wp-content/uploads/2017/10/AAAI\\_NAVIGATE\\_I\\_EDS-FLU\\_CRSwNP.pdf](http://www.optinose.com/wp-content/uploads/2017/10/AAAI_NAVIGATE_I_EDS-FLU_CRSwNP.pdf). Accessed October 9, 2017

<sup>5</sup> Leopold D., Elkayam D., Messina J. et al. A randomized double-blind trial of fluticasone propionate exhalation delivery system (FLU-EDS) for treatment of chronic rhinosinusitis with nasal polyps (NAVIGATE II). The University of Vermont, Optinose. 2017 Available at: [http://www.optinose.com/wp-content/uploads/2017/10/NAVIGATE\\_II\\_FLU-EDS\\_for\\_CRSwNP.pdf](http://www.optinose.com/wp-content/uploads/2017/10/NAVIGATE_II_FLU-EDS_for_CRSwNP.pdf). Accessed October 9, 2017

<sup>6</sup> Nasonex Prescribing Information. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; March 2013. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/020762s0381b1.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020762s0381b1.pdf). Accessed October 13, 2017

<sup>7</sup> Filiaci F, Passali D, Puxeddu R, Schrewelius C. A randomized controlled trial showing efficacy of once daily intranasal budesonide in nasal polyposis. Rhinology. 2000 Dec;38(4):185-90. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11190754>. Accessed October 13, 2017

<sup>8</sup> Jankowski R, Klossek JM, Attali V, Coste A, Serrano E. Long-term study of fluticasone propionate aqueous nasal spray in acute and maintenance therapy of nasal polyposis. Allergy. 2009 Jun;64(6):944-50. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19298572>. Accessed October 13, 2017

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