

Class Review: Intranasal Allergy Drugs

Month/Year of Review: July 2015

Purpose for Class Review:

Prior authorization (PA) with clinical criteria has been in place for intranasal corticosteroids, antihistamines and mast cell stabilizers since 2002. However, these criteria have not been reviewed by the P&T committee since 2008. These drugs have received FDA approval for use in seasonal and/or perennial allergic rhinitis, which is not funded by the Oregon Health Plan (OHP). An updated evidence-based review of these intranasal inhalers for OHP-funded conditions is therefore needed to determine the appropriateness of the current criteria.

Research Questions:

- For adults and children with conditions funded by the OHP, which conditions have nasal inhalers been studied to treat?
- Do nasal corticosteroids, antihistamines or mast cell stabilizers differ in effectiveness when used to treat conditions funded by the OHP?
- Do nasal corticosteroids, antihistamines or mast cell stabilizers differ in safety when used to treat conditions funded by the OHP?
- Are there subgroups of patients based on demographics (e.g., age, race, gender), concomitant comorbidities and medications, or pregnancy status, for which one nasal inhaler is more effective or associated with fewer harms?

Conclusions:

- There is moderate quality evidence intranasal corticosteroids are effective in managing asthma-related outcomes in patients who are not concurrently receiving an orally inhaled corticosteroid. An improvement in forced expiratory volume in 1 second (FEV1) (2.10%; 95% CI, 0.21 to 3.99%), asthma-related symptom scores (0.69; 95% CI, 0.04 to 1.25), and use of rescue asthma medication (standardized mean difference [SMD] 0.22; 95% CI, 0.04 to 0.39) was observed in patients receiving an intranasal corticosteroid relative to placebo. However, in patients already on an orally inhaled corticosteroid, there is moderate strength of evidence the addition of an intranasal corticosteroid does not offer any additional benefit in any asthma-related outcome.¹
- There is low quality evidence that intranasal corticosteroids reduce apneas and hypoapneas, without improving nadir oxygen saturation, by demonstration of improvement in the Apnea Hypopnea Index (AHI) following short-term therapy in children and adults with obstructive sleep apnea (OSA).^{2,3} The AHI is calculated by dividing the number of apnea events by the number of hours of sleep. There is also low quality evidence intranasal corticosteroids do not result in complete cessation of apneas or hypoapneas, do not improve subjective sleep quality, and do not prolong total sleep time in treated patients.^{2,3}
- There is moderate quality evidence that patients receiving intranasal corticosteroids are more likely to experience resolution or improvement in symptoms of acute sinusitis at 21 days of treatment compared to placebo (73% versus 66.4%; risk ratio (RR) 1.11; 95% CI, 1.04 to 1.18).⁴ The efficacy of intranasal corticosteroids for acute sinusitis appears to be delayed as there is moderate quality evidence that use of intranasal corticosteroids for a period of less than 21 days does not result in any difference in resolution or improvement in symptoms of acute sinusitis compared to placebo.⁵

- There is moderate quality evidence that when compared to placebo, topical corticosteroids improve symptom scores in patients with chronic rhinosinusitis (SMD -0.37; 95% CI, -0.60 to -0.13, p=0.002) and results in greater response to therapy (RR 1.69; 95% CI, 1.21 to 2.37, p=0.002). Subgroup analyses by topical delivery method revealed more benefit when the corticosteroid was administered directly to the sinuses than with simple nasal delivery (p=0.04).⁶
- Evidence is insufficient to draw any conclusions about comparative effectiveness, efficacy, or safety between intranasal corticosteroid formulations for management of asthma-related outcomes, obstructive sleep apnea, acute sinusitis and chronic rhinosinusitis.
- Evidence is insufficient for the intranasal use of antihistamines or mast cell stabilizers for any indication other than allergic rhinitis.
- There is moderate quality evidence that intranasal corticosteroids, antihistamines and mast cell stabilizers are not associated with increased serious harms compared to placebo. However, use of intranasal corticosteroids in growing children may be associated with increased risk for growth suppression.⁷

Recommendations:

- Create a PDL for “Intranasal Allergy Drugs”.
- Make fluticasone propionate (Legend only) a preferred drug on the PDL and all other intranasal corticosteroids non-preferred.
- Make non-steroid intranasal allergy drugs non-preferred due to lack of evidence for OHP-funded conditions.
- Restrict use of non-preferred intranasal corticosteroids for OHP-funded conditions as outlined in the PA criteria in **Appendix 3**.

Background:

Each intranasal formulation of drugs within the corticosteroid, antihistamine and mast cell stabilizer classes have demonstrated benefit, and received FDA approval, for allergic rhinitis (see **Table 1**).⁸ However, treatment of allergic and chronic rhinitis and nasal polyps are not currently funded by the OHP.

Intranasal formulations of these drugs are well tolerated and are associated with various topical adverse effects in 5-10% of patients regardless of the formulation.⁹ The most common of these adverse side effects include dryness, burning, hoarseness, sneezing, and aftertaste. A common precaution for intranasal corticosteroids includes potential reduction in growth velocity in children.⁷

Intranasal use of antihistamines and mast cell stabilizers has not been adequately studied in conditions outside of allergic rhinitis. However, intranasal corticosteroids have been studied and used for several other conditions that are currently funded by the OHP. For example, allergic rhinitis and asthma are often comorbid diseases. An epidemiologic association between allergic rhinitis and asthma has been consistently demonstrated across patient populations. Given the association, it is hypothesized that reducing inflammation in the upper airway with an intranasal corticosteroid may improve asthma symptoms.¹ Attempts have also been made to reduce frequency of episodes of OSA by changing the characteristics of the upper airway using topical therapies such as intranasal corticosteroids.² Acute sinusitis is frequently caused by a viral infection and is a common reason for primary care visits. Inflammation of nasal mucosa plays an essential role in the development of sinusitis. In addition to treating seasonal and perennial rhinitis, corticosteroids might be beneficial in reducing inflammation in the treatment of sinusitis.⁴ Lastly, chronic rhinosinusitis (CRS) is a group of disorders characterized by chronic inflammation of the mucosa of the nose and paranasal sinuses, with symptoms that persist for more than 12 weeks without complete resolution of symptoms. Anti-inflammatory therapies, including intranasal corticosteroids, play a significant role in the treatment of CRS.⁶ The efficacy and safety of intranasal corticosteroids for the management of these conditions will therefore be reviewed.

Table 1. Indications and Dosing.⁸

Drug Name (Trade Name)	FDA Indication(s)	Formulation	OTC
Intranasal Antihistamines			
Azelastine (ASTEPRO, generic)	Allergic Rhinitis ≥6 mo	0.125 and 0.1876 mg/spray	NO
Olopatadine (<i>generic</i> , PATANSASE)	Allergic Rhinitis ≥6 yo	0.665 mg/spray	NO
Intranasal Corticosteroids			
Azelastine-Fluticasone propionate (DYMISTA)	Allergic Rhinitis ≥6 yo	0.125 mg-0.05 mg/spray	NO
Beclomethasone (BECONASE AQ)	Allergic, non-allergic rhinitis ≥6 yo	0.042 mg/spray	NO
Beclomethasone (QNASL)	Allergic rhinitis ≥4 yo	0.04 and 0.08 mg/spray	NO
Budesonide (<i>generic</i> , RHINOCORT, RHINOCORT ALLERGY)	Allergic Rhinitis ≥6 yo	0.032 mg/spray	YES
Ciclesonide (OMNARIS)	Allergic Rhinitis ≥6 yo	0.05 mg/spray	NO
Ciclesonide (ZETONNA)	Allergic Rhinitis ≥12 yo	0.037 mg/spray	NO
Flunisolide (<i>generic</i>)	Allergic Rhinitis ≥6 yo	0.025 and 0.029 mg/spray	NO
Fluticasone furoate (VERAMYST)	Allergic Rhinitis ≥2 yo	0.0275 mg/spray	NO
Fluticasone propionate (FLONASE, FLONSASE ALLERGY RELIEF, <i>generic</i>)	Allergic Rhinitis ≥4 yo	0.5 mg/spray	YES
Mometasone (NASONEX)	Allergic Rhinitis ≥2 yo; Nasal Polyps ≥18 yo	0.05 mg/spray	NO
Triamcinolone (<i>generic</i> ; NASACORT ALLERGY 24 HOUR)	Allergic Rhinitis ≥2 yo	0.055 mg/spray	YES
Intranasal Mast Cell Stabilizers			
Cromolyn (<i>generic</i>)	Allergic Rhinitis ≥2 yo	5.2 mg/spray	YES

Abbreviations: mo = months of age; OTC = over-the-counter; yo = years of age

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls in conditions funded by the OHP were conducted. The Medline search strategy used for this review is available in **Appendix 1**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will only be emphasized if evidence is insufficient from preferred sources.

Systematic Reviews:

Asthma

A systematic review¹ with meta-analysis sought to assess the impact of intranasal corticosteroids on asthma outcomes in patients with allergic rhinitis and comorbid asthma. There were 18 eligible studies (n=1,659) identified that met inclusion criteria. All trials were placebo-controlled, single- or double-blinded RCTs or appropriate crossover trials, evaluating the efficacy of intranasal corticosteroids in adults or children which assessed at least one asthma-specific clinical outcome measure. Ten studies assessed primarily adult patients, 5 only recruited pediatric patients, and 3 studies enrolled both adults and children into the trials. The included studies appeared to have an overall low risk of bias. Ten of the 18 trials measured changes in FEV1. Pooling data from these trials found a significant improvement in percent-predicted FEV1 of 2.10% (95% CI, 0.21% to 3.99%) with use of an intranasal corticosteroid but a non-significant improvement in change in FEV1 when expressed in Liters (0.09 L; 95% CI, 0.04 to 0.22 L). Subgroup analyses demonstrated that there was a more pronounced treatment effect in patients who did not receive concurrent treatment with an orally inhaled corticosteroid (SMD = 0.31; 95% CI, 0.04 to 0.58), whereas an intranasal corticosteroid treatment had no impact on FEV1 in patients who received a concurrent orally inhaled corticosteroid (SMD 0.04; 95% CI, -0.15 to 0.22). No difference was found when morning oral peak expiratory flow (PEF) was assessed, whether patients were concurrently receiving an orally inhaled corticosteroid or not. In trials reporting asthma symptom scores using various scales, a significant improvement in symptom scores of 0.69 (95% CI, 0.04 to 1.25) were demonstrated in patients receiving intranasal corticosteroids versus placebo. However, similar to other subgroup analyses, there was no statistical difference between those receiving an intranasal corticosteroid and those receiving placebo in patients who concurrently received an orally inhaled corticosteroid. When quality of life was assessed, there was a non-significant improvement demonstrated in patients who received an intranasal corticosteroid compared to patients who received placebo (mean difference = -0.04 QoL units; 95% CI, -0.42 to 0.49). Lastly, a significant improvement in use of rescue medication (i.e., albuterol) was demonstrated in patients who received intranasal corticosteroids versus placebo (SMD 0.22; 95% CI, 0.04 to 0.39). But again, similar to other subgroup analyses, the difference was more profound in patients who did not concurrently take an orally inhaled corticosteroid (SMD 0.29; 95% CI, 0.01 to 0.58), and the difference was lost in patients who did receive an orally inhaled corticosteroid (SMD 0.00; 95% CI, -0.14 to 0.15).¹

Obstructive Sleep Apnea

A systematic review³ evaluated the evidence of anti-inflammatory drugs as treatment for OSA in children. Only two placebo-controlled RCTs were identified that specifically investigated the efficacy of intranasal corticosteroids (fluticasone and budesonide). The authors excluded a substantial number of potentially useful trials from the review because of the absence of polysomnographic assessment (sleep study) to ascertain the presence and severity of OSA. The first trial showed a statistically significant reduction of the Apnea Hypopnea Index (AHI) following six weeks of fluticasone (the AHI is calculated by dividing the number of apnea events by the number of hours of sleep). Users of fluticasone experienced a significantly greater reduction in AHI after six weeks compared to placebo. However, the study was small (n=25) and was terminated prematurely. Other study limitations were that treatment resulted only in a reduction of apneas and hypopneas, not in their complete cessation. In addition, the nadir oxygen saturation did not change following treatment. Thus, the children may have continued to have sleep-related hypoxia of the same magnitude as before treatment. Lastly, this study investigated neither sustained treatment effect over the long-term nor potential long-term harms, such as growth suppression. The second trial also reported a significant reduction in AHI with budesonide compared to placebo but did not analyze the patients as randomized. There were other methodological issues as well; baseline imbalances were not accounted for in the analysis and there was a higher number of withdrawals in the placebo group. The evidence from the two studies primarily applies to children with mild to moderate OSA. In these patients, intranasal fluticasone may have a short-term beneficial effect on the AHI in children with mild to moderate OSA but the evidence is very limited so far.³

A second systematic review² evaluated drug therapy for OSA in adults. The review identified one placebo-controlled crossover trial (n=24) evaluating intranasal fluticasone in patients with OSA and concurrent allergic rhinitis. In the study, fluticasone led to a significantly lower AHI compared with placebo (23.3 versus 30.3; p<0.05). For reference, scores between 15 and 29 are categorized as *moderate* sleep apnea while scores of 30 or higher are categorized as *severe* sleep apnea. No significant differences in subjective sleep quality, total sleep time and nocturnal oxygen saturation were apparent. Participants reported an increase in daytime alertness but no validated scale was used. From these data, intranasal fluticasone can reduce apnea in adult patients with mild OSA and co-existing rhinitis, but more evidence of long-term effectiveness is lacking.²

Acute Sinusitis

A systematic review⁴ examined whether intranasal corticosteroids are effective in relieving symptoms of acute sinusitis in adults and children. Eligible studies were RCTs comparing intranasal corticosteroids of any dose to placebo or no intervention in adults and children with acute sinusitis. Acute sinusitis was defined by clinical diagnosis and confirmed by radiological evidence or nasal endoscopy. The primary outcome was the proportion of patients with either resolution or improvement of symptoms. Four double-blind, randomized, placebo-controlled studies of 15 or 21 days' duration involving 1,943 patients with acute sinusitis met the inclusion criteria. Results of 3 trials were combined for meta-analysis (the fourth study was not included due to high attrition, use of non-parametric tests, and inability to extract data), patients receiving intranasal corticosteroids were more likely to experience resolution or improvement in symptoms (73% vs. 66.4%; RR 1.11; 95% CI, 1.04 to 1.18).⁴

A second systematic review with meta-analysis⁵ evaluated RCTs comparing intranasal corticosteroids with placebo in children or adults who had clinical signs and symptoms acute sinusitis or rhinosinusitis. Six studies (n=2,495) met inclusion criteria, all of which had adequate allocation concealment, blinding, and comparability of groups; however, 3 studies did not report the method of randomization. In 5 RCTs that assessed resolution or improvement of symptoms at days 14 to 21, intranasal corticosteroids had a modest clinical benefit, with a risk difference of 0.08 (95% CI, 0.03 to 0.13). However, this benefit was driven by studies of 21 days' duration; there was no significant difference found in studies of 14 or 15 days' duration. In studies that reported symptom relief, patients who received intranasal corticosteroids had significantly greater improvement in facial pain, congestion, rhinorrhea, headache and post-nasal drip compared to patients who received placebo (all p<0.05). Adverse events were mild or moderate in severity but there were no significant differences of reported events between patients who took intranasal corticosteroids (23%) and patients who took placebo (23%).⁵

Chronic Rhinosinusitis

A systematic review⁶ assessed the effects of topical corticosteroid treatment in patients with chronic rhinosinusitis (CRS) without nasal polyps. The primary outcome was sinonasal symptoms, which was measured by symptom scores, proportion of patients showing improvement of symptoms, or quality of life measures. A meta-analysis of symptom improvement data was performed, including subgroup analysis by topical delivery methods. Eligible studies for inclusion were all randomized trials in which a topically administered corticosteroid was compared with either a placebo, no treatment, or an alternative topically administered corticosteroid for the treatment of CRS without polyps in patients of any age. Ten studies (590 patients) met the inclusion criteria. The trials were of low (six trials) and medium (four trials) risk of bias. When compared to placebo, topical corticosteroids improved symptom scores (SMD -0.37; 95% CI, -0.60 to -0.13, p=0.002) and had a greater proportion of responders (RR 1.69; 95% CI, 1.21 to 2.37, p=0.002). Subgroup analyses by topical delivery method revealed more benefit when the corticosteroid was administered directly to the sinuses than with simple nasal delivery (p=0.04). There were no differences between the groups in quality of life or adverse events.⁶

Guidelines:

The American Academy of Pediatrics has published a clinical practice guideline on the management of OSA in children.¹⁰ Within the guideline, the panel addresses use of intranasal corticosteroids. The guideline suggests intranasal corticosteroids are an option for children with mild OSA (AHI <5 per hour) in whom adenotonsillectomy is contraindicated or for mild post-operative OSA (Evidence Quality: *B*; Recommendation Strength: *Option*). Though studies demonstrate the use of intranasal corticosteroids decreases the degree of OSA, residual OSA may often remain. Indeed, some children may not have an adequate response to intranasal corticosteroids and it is unknown whether the therapeutic effect persists long-term. The panel agreed based on the evidence that intranasal corticosteroids provide a less invasive treatment than surgery or CPAP and, therefore, may be preferred in some cases despite inferior efficacy and lack of long-term efficacy data.¹⁰

Clinical Trials:

Several potentially relevant abstracts were reviewed from the literature search.

After further review, 5 trials of intranasal corticosteroids were potentially relevant: 3 trials evaluated subjects with asthma and 2 trials evaluated subjects with sleep apnea. One of the sleep apnea studies was not randomized. However, because high-quality systematic reviews for this population are already available, these studies are presented as abstracts in **Appendix 2**.

No studies were identified that evaluated intranasal antihistamines or mast cell stabilizers for OHP-funded conditions. A Medline search of current non-preferred oral antihistamines found inconsistent evidence for these drugs in improving asthma-related outcomes. Oral antihistamines were not effective in patients with OSA. There is insufficient evidence for use of oral antihistamines for other conditions funded by the OHP. For completeness, identified studies are presented as abstracts in **Appendix 2**. Oral antihistamines designated as preferred on the PDL are available without prior authorization.

References:

1. Lohia S, Schlosser R, Soler Z. Impact of intranasal corticosteroids on asthma outcomes in allergic rhinitis: a meta-analysis. *Allergy*. 2013;68:569-579.
2. Mason M, Welsh E, Smith I. Drug therapy for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev*. 2013;(5):CD003002. doi:10.1002/14651858.CD003002.pub3.
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5. Hayward G, Heneghan C, Perera R, Thompson M. Intranasal corticosteroids in management of acute sinusitis: a systematic review and meta-analysis. *Ann Fam Med*. 2012;10:241-249. doi:10.1370/afm.1338.
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9. Petty D, Blaiss M. Intranasal corticosteroids topical characteristics: side effects, formulation, and volume. *Am J Rhinol Allergy*. 2013;27:510-513. doi:10.2500/ajra.2013.27.3949.
10. Marcus C, Brooks L, Draper K, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics*. 2012;130:576-584.

Appendix 1: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to May Week 3 2015

- 1 exp Beclomethasone/ 1421
- 2 exp Budesonide/ 3044
- 3 ciclesonide.mp. 273
- 4 flunisolide.mp. 191
- 5 fluticasone.mp. 3128
- 6 mometasone.mp. 662
- 7 exp Triamcinolone Acetonide/ or exp Triamcinolone/ 3835
- 8 exp Nasal Absorption/ or exp Nasal Sprays/ or nasal.mp. 58239
- 9 exp Administration, Intranasal/ 8152
- 10 8 or 9 62254
- 11 1 or 2 or 3 or 4 or 5 or 6 or 7 11265
- 12 10 and 11 1138
- 13 exp Asthma/ 60783
- 14 exp Sleep Apnea Syndromes/ or exp Sleep Apnea, Central/ or exp Sleep Apnea, Obstructive/ 19814
- 15 exp Sinusitis/ 9419
- 16 13 or 14 or 15 89228
- 17 12 and 16 243

Ovid MEDLINE(R) without Revisions 1996 to May Week 3 2015

- 1 azelastine.mp. 327
- 2 olopatadine.mp. 254
- 3 exp Cromolyn Sodium/ 768
- 4 exp Sleep Apnea Syndromes/ 19814
- 5 exp Sinusitis/ 9419
- 6 exp Asthma/ 60783
- 7 exp Nasal Absorption/ or exp Nasal Sprays/ or nasal.mp. 58239
- 8 exp Administration, Intranasal/ 8152
- 9 1 or 2 or 3 1311
- 10 4 or 5 or 6 89228
- 11 7 or 8 62254
- 12 9 and 10 and 11 15

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to May Week 4 2015

- 1 exp Cetirizine/ 1152
- 2 exp Loratadine/ 1014
- 3 fexofenadine.mp. 693
- 4 levocetirizine.mp. 277
- 5 desloratadine.mp. 454
- 6 1 or 2 or 3 or 4 or 5 2655
- 7 exp Asthma/ 108998
- 8 exp Bronchial Hyperreactivity/ 6928
- 9 exp Inflammation/ and exp Orbital Diseases/ 1264
- 10 exp Frontal Sinusitis/ or exp Sphenoid Sinusitis/ or exp Ethmoid Sinusitis/ or exp Sinusitis/ or exp Maxillary Sinusitis/ 16762
- 11 exp Sleep Apnea Syndromes/ 25245
- 12 exp Granulomatosis with Polyangiitis/ 5953
- 13 7 or 8 or 9 or 10 or 11 or 12 159158
- 14 azelastine.mp. 595
- 15 olopatadine.mp. 266
- 16 exp Cromolyn Sodium/ 3989
- 17 14 or 15 or 16 4799
- 18 6 or 17 7365
- 19 13 and 18 2103
- 20 limit 19 to (english language and humans and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 673

Appendix 2: Abstracts

Intranasal Corticosteroids, Asthma

Baiardini I, Villa E, Rogkakou A, et al. Effects of mometasone furoate on the quality of life: a randomized placebo-controlled trial in persistent allergic rhinitis and intermittent asthma using the Rhinasthma questionnaire. *Clinical & Experimental Allergy*. 2010;41:417–423.

BACKGROUND: Allergic rhinitis, especially when persistent (PER) and associated with asthma heavily impairs patients' quality of life (QoL). **OBJECTIVE:** This study assessed the effect of mometasone furoate nasal spray (MFNS) on the QoL of patients with PER and asthma, using the Rhinasthma questionnaire (EUDRACT n. 2007-004683-45). **METHODS:** Patients with moderate/severe PER and intermittent asthma were randomized to MFNS (alcohol-free) 200 mg/day or placebo for 28 days. Rhinasthma was completed at baseline and at weeks 2 and 4. The total five symptom score (T5SS) for rhinitis, the asthma symptom score and the sum of the two [global symptoms score (GSS)] were recorded daily. The primary outcome was the change in the Rhinasthma global summary (GS) at the end of treatment. Secondary end-points were (a) the change from baseline to end of treatment of each Rhinasthma factor: upper airways (UAs), lower airways (LAs) and respiratory allergy impact; (b) the change from baseline to end of treatment of the T5SS and of the GSS and (c) the use of rescue medication. **RESULTS:** Fifty-two adults were randomized. Compared with placebo, MFNS produced a significant change in the Rhinasthma GS (-10.4 vs. 0.4; $P<0.01$). MFNS also achieved a significant improvement of the UA (-16.6 vs. 0.1; $P<0.001$), LA (-10.8 vs. 1.1; $P<0.001$) and GSS (-6.7 vs. -3.1; $P=0.019$). The change of the T5SS was greater in the MFNS group but did not reach statistical significance. **Conclusion** In patients with PER rhinitis and intermittent asthma, MFNS improves the QoL and the burden of respiratory symptoms. Treating rhinitis may affect the asthma-related QoL.

Kersten E, van Leeuwen J, Brand P, et al. Effect of an Intranasal Corticosteroid on Exercise Induced Bronchoconstriction in Asthmatic Children. *Pediatric Pulmonology*. 2012;47:27-35.

RATIONALE: Allergic rhinitis and exercise induced bronchoconstriction (EIB) are common in asthmatic children. The aim of this study was to investigate whether treatment of allergic rhinitis with an intranasal corticosteroid protects against EIB in asthmatic children. **METHODS:** This was a double-blind, randomized, placebo-controlled, parallel group study. Subjects aged 12–17 years, with mild-to-moderate asthma, intermittent allergic rhinitis and $>10\%$ fall in FEV1 at a screening exercise challenge were randomized to 22 \pm 3 days treatment with intranasal fluticasone furoate or placebo. The primary outcome was change in exercise induced fall in FEV1. Secondary outcomes were changes in the area under the curve (AUC), asthma control questionnaire (ACQ), pediatric asthma quality of life questionnaire (PAQLQ), and exhaled nitric oxide (FeNO). **RESULTS:** Twenty-five children completed the study. Mean exercise induced fall in FEV1 (\pm SD) decreased significantly (95% CI, 0.7-18.2%; $P=0.04$) in the fluticasone furoate group from 28.4 \pm 15.8% to 19.0 \pm 13.8%, compared to the placebo group (27.4 \pm 16.0% to 27.4 \pm 19.2%). The change in AUC was not significantly different between treatment groups. However, within the fluticasone furoate group the AUC decreased significantly ($P=0.01$). Although total PAQLQ score did not improve, the activity limitation domain score improved significantly within the fluticasone furoate group ($P=0.03$). No significant changes were observed in FeNO and ACQ. **CONCLUSION:** Treatment of allergic rhinitis in asthmatic children with an intranasal corticosteroid reduces EIB and tends to improve quality of life.

Scichilone N, Arrigo R, Paterno A, et al. The Effect of Intranasal Corticosteroids on Asthma Control and Quality of Life in Allergic Rhinitis with Mild Asthma. *Journal of Asthma*. 2011;48:41-47.

BACKGROUND. The mechanisms through which rhinitis affects asthma have not been completely elucidated. We explored whether the effect of nasal treatment on asthma control and respiratory-related quality of life (HRQoL) is mediated by inflammatory changes of the upper and lower airways. **METHODS.** Allergic

rhinitics with mild asthma were randomized to a 14-day treatment period with either nasal budesonide 100 mcg, 1 puff per nostril twice a day, or placebo. Clinical, functional, and biological evaluations were performed before and after treatment. RESULTS. Twenty subjects (M/F: 10/10; age: 31 ±15 years; mean ±SD) were enrolled, and a total of 17 individuals completely participated in the study. Lung function was within the normal range. The total asthma control test (ACT) score was 20 ±5.3 and the RHINASTHMA Global Summary (GS) was 44 ± 15. The percentage proportion of eosinophils in nasal lavage was 9.9% and significantly correlated with spirometric parameters reflecting peripheral airway function (for FEF₅₀: r=0.48, p=0.03; for FEF₂₅: r=0.47, p=0.03). The pH of the exhaled breath condensate (EBC) was 7.33 ±0.4. After nasal treatment, the percentage proportion of eosinophils fell significantly (p=0.002), and changes in percentage proportion of eosinophils were associated with changes both in the ACT score (r=0.76, p=0.04) and in the RHINASTHMA GS (r=0.77, p=0.02). The increase in the pH of the EBC was not associated with changes in the ACT score or with the RHINASTHMA GS. CONCLUSIONS. These findings confirm that, in subjects with allergic rhinitis with mild asthma, nasal inflammation impacts on asthma control and HRQoL. The improved control of respiratory symptoms obtained with nasal corticosteroids seems to be mediated by functional changes in the peripheral airways.

Intranasal Corticosteroids, Sleep Apnea

Lavigne F, Petrof B, Johnson J, et al. Effect of topical corticosteroids on allergic airway inflammation and disease severity in obstructive sleep apnoea. *Clinical & Experimental Allergy*. 2013;43:1124-1133.

BACKGROUND: The incidence of sleep-related breathing disorders is correlated with lower and upper airway inflammatory diseases, such as asthma and allergic rhinitis. We hypothesized that corticosteroids treatment would lead to a greater reduction in disease severity in obstructive sleep apnea syndrome (OSAS) patients with concomitant allergic rhinitis vs. non-allergic OSAS patients by reducing the level of inflammation in upper airway tissues. OBJECTIVE: This study was performed to determine whether treatment with intranasal corticosteroids could reduce upper airway inflammation and improve sleep parameters in obstructive sleep apnea syndrome patients with or without concomitant allergic rhinitis. METHODS: Obstructive sleep apnea syndrome patients with (n=34) or without (n=21) documented allergic rhinitis voluntarily enrolled in the study and were assessed at baseline and after corticosteroids treatment for 10-12 weeks. Sleep studies were performed and biopsies were obtained from the inferior turbinate, nasopharynx, and uvula. The apnea-hypopnea index, sleep quality, and level of daytime alertness were determined, and immunocytochemistry was used to phenotype tissue inflammation. RESULTS: Standard sleep indices improved following treatment in the entire cohort of obstructive sleep apnea syndrome patients, with greater improvement seen in the allergic rhinitis group. Allergic rhinitis patients demonstrated significantly improved O₂ saturation and a lower supine apnea-hypopnea index score after corticosteroid treatment; similar improvements were not seen in the non-allergic rhinitis group. Eosinophilia was detected at all three sites in the allergic rhinitis group, but not in the non-allergic rhinitis group. Following treatment, fewer eosinophils and CD4 lymphocytes were documented at all three biopsy sites in the allergic group; the reduction in inflammation was less apparent in the non-allergic rhinitis group. CONCLUSION: This study has provided important molecular and clinical evidence regarding the ability of corticosteroids to reduce upper airway inflammation and improve obstructive sleep apnea syndrome morbidity patients with concomitant allergic rhinitis.

Strobel W, Schlageter M, Andersson M, et al. Topical nasal steroid treatment does not improve CPAP compliance in unselected patients with OSAS. *Respiratory Medicine*. 2011; 105:310-315.

BACKGROUND: Continuous positive airways pressure (CPAP) for treatment of obstructive sleep apnea (OSA) can produce troublesome nasal symptoms (i.e. congestion, rhinorrhea) that may reduce the compliance of CPAP. Topical nasal steroids are often prescribed to reduce these side effects, although scientific data are scarce supporting any benefits of this treatment for CPAP-induced nasal side effects. OBJECTIVE: To study whether a topical nasal steroid can reduce

CPAP-induced nasal symptoms and improve CPAP adherence during the initial phase of OSA treatment. METHODS: A randomized, double-blinded, placebo-controlled study with fluticasone propionate 100 mg/nasal cavity twice daily Treatment was started 10 days prior to and continued throughout the first 4 weeks of CPAP. Sixty-three patients who were selected for CPAP treatment participated. Nasal symptoms were recorded, nasal patency was assessed and lung function was measured with a peak flow meter. The patients' adherence to CPAP was recorded by the CPAP device. RESULTS: Total nasal symptoms increased from baseline to 4 wks after CPAP use for both nasal treatments ($p < 0.05$). No differences in total nasal symptoms between treatments were seen ($p = 1$), and no differences in nasal peak flow values after treatment were seen ($p = 0.11$). Moreover, there were no differences in CPAP use between the treatments. CONCLUSION: fluticasone propionate as a nasal topical steroid does not reduce CPAP-induced unwanted nasal side effects, and has no beneficial effect on CPAP compliance during the first four weeks of treatment in unselected patients with OSAS.

Oral Antihistamines, Asthma

Lu S, Liu N, Dass B, et al. A Randomized Study Comparing the Effect of Loratadine Added to Montelukast with Montelukast, Loratadine, and Beclomethasone Monotherapies in Patients with Chronic Asthma. *Journal of Asthma*. 2009; 46:465-469. DOI: 10.1080/02770900902846323.

BACKGROUND. Loratadine added to montelukast has been suggested to improve endpoints of asthma. Objective. This study investigated the additive effects of concomitant montelukast and loratadine when compared with montelukast, loratadine, and inhaled beclomethasone monotherapies in asthma. METHODS. Patients ($n = 406$) were 15 to 65 years of age with a forced expiratory volume in 1 second (FEV1)-predicted of 50% to 85%, FEV1 reversibility $\geq 15\%$, and a minimal level of daytime symptoms and β -agonist use. This three-part 2X2 crossover-study consisted of two double-blind 6-week treatment periods where patients were administered once daily oral montelukast 10 mg, loratadine 10 mg, montelukast 10 mg + loratadine 10 mg, or twice daily inhaled beclomethasone 200 mcg. A subsequent 48-week extension study compared montelukast+loratadine with beclomethasone. The primary endpoint was the percentage change from baseline in FEV1. RESULTS. Over 6 weeks of double-blind treatment, significant improvements ($p < 0.05$) in the primary endpoint of FEV1 were seen for montelukast+loratadine versus loratadine (least-square mean percentage-point difference of 5.8%), beclomethasone versus montelukast+loratadine (2.35%), montelukast versus loratadine (5.94%), and beclomethasone versus montelukast (4.65%); a numerical improvement ($p = 0.054$) was seen for montelukast+loratadine versus montelukast (1.60%). Significant improvements for montelukast+loratadine versus montelukast were seen in some secondary endpoints (evening peak expiratory flow, nocturnal asthma symptom score, nocturnal awakenings, and asthma-specific quality of life) but not others. Significant improvements in most endpoints except daytime asthma symptoms score were seen for montelukast+loratadine versus loratadine. In the extension study, both montelukast+loratadine and beclomethasone improved several endpoints. All treatments were generally comparable in the percentage of patients with clinical and laboratory adverse experiences. CONCLUSION. In this study, the addition of loratadine to montelukast produced a small numerical, but not statistically significant, improvement in FEV1 and, in general, no consistent improvement in other asthma endpoints. No improvement of montelukast+loratadine versus beclomethasone was seen in any endpoint.

Ngamphaiboon J, Wirawarn T, Thongkaew T. Prevention of recurrent wheezing in young children by loratadine compared with ketotifen. *Journal of the Medical Association of Thailand*. 2009;92:351-355.

BACKGROUND: Various trials showed benefit of the prophylactic agent ketotifen in prevention of recurrent wheezing in young children, but no such clinical trial with loratadine or comparison trial is available. OBJECTIVE: To study the efficacy and safety of loratadine syrup compared with ketotifen and placebo in prevention of recurrent wheezing in young children. METHODS: Randomized double-blind placebo controlled trial on 90 recurrent wheezing children aged less than 6 years old was done. Children were randomized to receive loratadine, ketotifen syrup, or placebo with dose of 0.25 mL/kg once a day for four months. Blood biochemistry (CBC, LFT) and EKG were performed pre and post treatment period. Assessment of symptoms--wheezing and night cough including use of

bronchodilators was done daily via patient diary card. Subjects were asked to do monthly visits to the clinic for physical examination. At those visits, the doctors questioned the patients about adverse event. RESULTS: Of the 90 children enrolled, 12 dropped out. Thus, 27 children remained in the loratadine, 26 in the placebo, and 25 in the ketotifen group. The demographic data were comparable among the three treatment groups. It was noted that wheezing decreased significantly at 2 months in the ketotifen ($p = 0.008$) and at 3 months in the loratadine ($p = 0.029$) but not in the placebo group. Coughing at night decreased significantly at 3 months in both the loratadine ($p = 0.005$) and the ketotifen ($p = 0.036$) group. The use of bronchodilator drug was significantly decreased at 2 months in the ketotifen ($p = 0.028$) and placebo ($p = 0.025$) group, and at 3 months in the loratadine ($p = 0.009$) group. Only a few patients had mild adverse events in all groups. CONCLUSION: Loratadine and ketotifen are safe and effective significantly in prevention of recurrent wheezing in young children.

Manjra A, Nel H, Maharaj B. Effect of Desloratadine on Patients with Allergic Rhinitis and Exercise-Induced Bronchoconstriction: A Placebo Controlled Study. *Journal of Asthma*. 2009;46:156-159.

BACKGROUND. Exercise induced broncho-constriction (EIB) is a significant problem in asthmatic patients. The link between allergic rhinitis and asthma is now well established. Patients with allergic rhinitis may have EIB. OBJECTIVE. This study compared the effects of desloratadine and placebo on EIB in a group of patients with allergic rhinitis and EIB. METHODS. This was a double blind placebo controlled, randomized, crossover study. Exercise challenge tests were performed before and after 7 days of treatment with either 5 mg desloratadine or placebo. Patients then underwent a washout period for 7 days and were crossed over to receive either 5 mg desloratadine or placebo. The exercise challenge tests were repeated. RESULTS. Desloratadine had no effect on the reduction in percentage fall in FEV₁, the AUC (0–60 min) and the time to recovery. CONCLUSIONS. Desloratadine has no effect in attenuating the bronchoconstriction caused by exercise in patients with allergic rhinitis and exercise induced bronchoconstriction.

Pasquali M, Baiardini I, Rogkakou A. Levocetirizine in persistent allergic rhinitis and asthma: effects on symptoms, quality of life and inflammatory parameters. *Clinical and Experimental Allergy*. 2006;36:1161-67.

BACKGROUND: Levocetirizine (LCZ) has been shown to be effective in allergic rhinitis. We evaluated its clinical efficacy, anti-inflammatory actions and its effects on quality of life (QoL) with a specific instrument in the asthma–rhinitis comorbidity. METHODS: Fifty adult patients with persistent rhinitis with/without asthma were enrolled. After a 1-week run-in for baseline evaluation, they were randomized to LCZ or placebo for 8 weeks. Cromolyn and salbutamol were permitted on demand. Rhinoconjunctivitis and asthma symptoms were evaluated by diary cards. QoL was assessed by the specific Rhinasthma questionnaire and the generic SF-36 at different time-points. Nasal scrapings and lavages were also performed for inflammatory cell count and mediator assessment. RESULTS: Ten patients dropped out for unrelated reasons and the remaining completed the study with no side-effect. Symptoms began to decrease in the active group at the second week of treatment when the difference with the placebo group became significant (0.05) and so remained until the end of the trial. Starting from 2 weeks of therapy, there was a significant decrease vs. baseline in all the four components of the Rhinasthma questionnaire only in the active group. The intergroup comparison became significant ($P=0.05$) at 4 weeks. The SF-36 detected only sporadic differences between groups. Eosinophils and neutrophils in nasal scraping were significantly decreased in the LCZ group vs. baseline at all times. Nasal mediators were under the detection limits and no analysis could be performed. In the active group, only two patients used rescue medications compared with 13 patients in the placebo group. CONCLUSIONS: LCZ is clinically effective and capable of improving the rhinitis–asthma-related QoL.

Davis B, Todd D, Cockcroft W. Effect of combined montelukast and desloratadine on the early asthmatic response to inhaled allergen. *Journal of Allergy & Clinical Immunology*. 2005;116:768-72.

BACKGROUND: The early asthmatic response (EAR) to inhaled allergen results from IgE-mediated release of multiple mast-cell mediators, including leukotrienes and histamine, both of which cause bronchoconstriction. Combination therapy directed at blocking the effects of both mediators might protect against the EAR

better than either therapy alone. OBJECTIVE: We sought to evaluate the effect of desloratadine and montelukast, administered alone and in combination, on the EAR to inhaled allergen. METHODS: Ten adults with mild-to-moderate atopic asthma participated in a randomized, 4-way crossover study design comparing placebo, 5 mg of desloratadine, 10 mg of montelukast, and the combination administered at 26 hours and 2 hours before each allergen challenge conducted at least 7 days apart. The primary end point was the concentration of allergen that resulted in a 20% decrease in FEV1 (PC20). RESULTS: The geometric mean allergen PC20 (mean log +/- SEM) for combination therapy, montelukast, desloratadine, and placebo was 697 U/mL (2.8433 +/- 0.3253), 338 U/mL (2.5295 +/- 0.2979), 123 U/mL (2.0883 +/- 0.2102), and 104 U/mL (2.0166 +/- 0.2553), respectively (n = 9; P < .00001, ANOVA). Montelukast increased the allergen PC20 4.8-fold, and combination therapy increased the allergen PC20 8.9-fold. The effect of the combination was greater than that with montelukast alone (P < .02). Desloratadine treatment was no different than placebo. CONCLUSIONS: The early response to inhaled allergen was unchanged after desloratadine therapy and partially inhibited with montelukast therapy. The combination of desloratadine and montelukast provided superior efficacy to either blocker administered alone. Investigations into the possible mechanisms of the enhanced inhibition are necessary.

Orhan F, Baki A. The bronchodilatory effects of loratadine, terbutaline, and both together versus placebo in childhood asthma. *Journal of Investigational Allergology & Clinical Immunology*. 2003;13:189-92.

AIM: To assess the bronchodilatory effect of loratadine in children with mild-to-moderate asthma and to determine whether loratadine interacts with terbutaline. METHODS: The effect on pulmonary functions of a 10 mg oral dose of loratadine, with and without inhaled terbutaline powder (0.5 mg), was determined in 13 patients with a mean (SE) age of 10.63 (0.77) years (range from eight to 17 years) at 11 time points during 8 h in a randomized, double-blind, placebo controlled, crossover study. Forced expiratory volume in 1 s (FEV1) was the primary measure of efficacy. RESULTS: Although loratadine alone produced an increase in FEV1 relative to baseline, this was not statistically significant (p > 0.05). Terbutaline with, and without loratadine, significantly increased FEV1 from 1 to 5 h according to baseline (p<0.004). When compared with the placebo, loratadine significantly increased FEV1 from 150 min to 8 h (p<0.05). Also, terbutaline alone, or in combination with loratadine, significantly increased FEV1 from 30 min to 7 h (p<0.004, from 30 min to 5 h; p<0.05, between 6-7 h). Although the mean increase in FEV1, with terbutaline + loratadine in combination, was greater than with terbutaline alone, the difference was not significant (p>0.05). CONCLUSION: Loratadine has a mild bronchodilatory effect in the study period and does not interfere with the bronchodilatory effect of terbutaline in childhood asthma.

Baena-Cagnania C, Bergerb W, DuBuske L, et al. Comparative Effects of Desloratadine versus Montelukast on Asthma Symptoms and Use of β 2-Agonists in Patients with Seasonal Allergic Rhinitis and Asthma. *Int Arch Allergy Immunol*. 2003;130:307-313. DOI: 10.1159/000070218

BACKGROUND: Asthma and seasonal allergic rhinitis (SAR) are recognized as manifestations of a single airway disease. Desloratadine has demonstrated efficacy in treating SAR symptoms, including nasal obstruction. METHODS: Safety and efficacy of desloratadine and montelukast each were assessed in a double-blind, placebo-controlled trial of patients with SAR and symptoms of asthma, who were assigned randomly to once-daily treatment with desloratadine 5 mg, montelukast 10 mg, or placebo for 4 weeks. Change from baseline of AM/PM reflective total asthma symptom severity scores (TASS), FEV1, individual asthma symptom scores, and β 2-agonist usage were assessed. RESULTS: Desloratadine and montelukast each were associated with statistically significant reductions from baseline in the mean TASS averaged over the 4-week period (p \leq 0.022 vs. placebo). Individual asthma symptom scores also improved significantly for both therapies (p \leq 0.05). Patients treated with desloratadine or montelukast demonstrated improvement from baseline in FEV1 versus placebo; significant improvement was seen in a subset of patients with baseline FEV1 <80% of predicted normal (both p<0.05). Both active therapies significantly reduced β 2-agonist use (both p<0.01). Improvements for both therapies were comparable for all efficacy parameters; they were tolerated well with adverse event profiles similar to placebo. CONCLUSIONS: Asthma symptoms and β 2-agonist were improved significantly in patients with concomitant SAR and asthma treated with desloratadine

5 mg as well as montelukast 10 mg once daily. Both therapies significantly improved FEV1 in a subset of patients with FEV1 <80% of predicted normal at entry. Improvements in asthma symptoms were comparable for both active treatment groups.

Oral Antihistamines, Sleep Apnea

Acar M, Cingi C, Sakallioğlu O, et al. The effects of mometasone furoate and desloratadine in obstructive sleep apnea syndrome patients with allergic rhinitis. *Am J Rhinol Allergy*. 2013;27:e113-e116. DOI 10.2500/ajra.2013.27.3921

BACKGROUND: Allergic rhinitis (AR) and obstructive sleep apnea syndrome (OSAS) are worldwide prevalent diseases. These diseases impair patient quality of life. The aim of this study was to investigate and compare the efficacy of treatment of AR on OSAS by objective and subjective methods. **METHODS:** The study group was composed of 80 OSAS patients with AR between the ages of 30 and 50 years. The patients were admitted with the complaint of snoring, and they were asked about AR-related symptoms (nasal discharge, nasal itching, sneeze, and nasal obstruction). Daytime somnolence was measured by the Epworth sleepiness scale (ESS). Sleep parameters on polysomnography tests before and after treatment were compared, and the effects of different AR treatment protocols on sleep quality were evaluated. **RESULTS:** When pretreatment and posttreatment apnea–hypopnea index (AHI) values of the groups were compared, the most significant difference was observed in the nasal steroid (Ns) plus antihistamine (Ah) group ($p < 0.05$). The ESS results were significantly decreased in the Ns and Ns+Ah groups after treatment ($p < 0.05$). AHI oxygen saturation <90% were significantly decreased in the Ns and Ns+Ah groups after treatment ($p < 0.05$). **CONCLUSION:** Nasal obstruction due to nasal congestion causes increases in airway resistance and can lead to development of OSAS. We concluded that treating AR with Ns has both positive effects on OSAS and daily activity. However, adding Ah to this treatment did not show improved effects compared with placebo treatment.

Intranasal Allergy Drugs

Goals:

- Restrict use of intranasal allergy inhalers for conditions funded by the OHP and where there is evidence of benefit.
- Treatment for allergic or non-allergic rhinitis is funded by the OHP only if it complicates asthma, sinusitis or obstructive sleep apnea. Only intranasal corticosteroids have evidence of benefit for these conditions.

Length of Authorization:

6 months

Requires PA:

- Non-preferred intranasal corticosteroids
- Intranasal antihistamines
- Intranasal cromolyn sodium

Covered Alternatives:

- Preferred alternatives listed at <http://orpd.org/drugs/>
- Preferred intranasal corticosteroids, preferred second generation antihistamines, and first generation antihistamines DO NOT require prior authorization.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Will the prescriber consider switching to a preferred product? <i>Note: preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.</i>	Yes: Inform provider of covered alternatives.	No: Go to #3
3. Is the prescribed drug an intranasal corticosteroid?	Yes: Go to #4	No: Pass to RPh; deny for medical appropriateness or not funded by OHP.
4. Does the patient have asthma or reactive airway disease exacerbated by chronic/allergic rhinitis (493.xx)?	Yes: Go to #5	No: Go to #6

Approval Criteria

<p>5. Does the drug profile show the patient is currently receiving an orally inhaled corticosteroid (ICS)?</p>	<p>Yes: Pass to RPh; deny for medical appropriateness.</p> <p>Note: asthma-related outcomes are not improved by the addition of an intranasal corticosteroid to an orally inhaled corticosteroid.</p>	<p>No: Approve for 6 months.</p>
<p>6. Does patient have other co-morbid conditions or complications that are funded by the OHP?</p> <ul style="list-style-type: none"> • Chronic Sinusitis (473.xx) • Acute Sinusitis (461.xx) • Sleep Apnea (327.20; 327.21; 327.23; 327.29; 780.51; 780.53; 780.57) 	<p>Yes: Document ICD-9 code(s) and approve for 6 months.</p>	<p>No: Go to #7</p>
<p>7. RPh only: Is the diagnosis funded by the OHP?</p>	<p>Funded: Deny for medical appropriateness.</p> <p>(e.g., COPD, Obstructive Chronic Bronchitis, or other Chronic Bronchitis [496; 490; 491.0; 491.1; 491.2x; 491.8; 491.9])</p> <p>Use clinical judgment to APPROVE for 1 month starting today to allow time for appeal.</p> <p>Message: “The request has been denied because it is considered medically inappropriate; however, it has been APPROVED for 1 month to allow time for appeal.”</p>	<p>Not Funded: Deny, not funded by the OHP.</p> <p>(e.g., allergic rhinitis (477.x), chronic rhinitis (472.0), allergic conjunctivitis (372.14), upper respiratory infection (465.9), acute nasopharyngitis (common cold) (460), urticaria (708.x), etc.)</p>

P&T / DUR Review: 7/15 (AG); 9/08; 2/06; 9/04; 5/04; 5/02
 Implementation: TBD; 8/09; 9/06; 3/06; 5/05; 10/04; 8/02