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## Asthma Controller Update

**Month/Year of Review:** May 2012 **End date of literature search:** April 2012
**PDL Class:** Asthma Controllers
**Preferred Agents**: Beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate (diskus and HFA), formoterol fumarate, mometasone furoate, montelukast sodium, salmeterol xinafoate, zafirlukast
**Non-preferred Agents**: Ciclesonide, triamcinolone acetonide, zileuton, arformoterol, formoterol fumarate/eformoterol, omalizumab, indacterol, mometasone/formoterol, fluticasone/salmeterol, budesonide/formoterol, mometasone/formoterol

Purpose of Review:
To update the evidence on efficacy and safety of available asthma controller medications since original evaluation presented March, 2010.

Previous Recommendations[1]:

1. Inhaled corticosteroids (ICS) are recommended for adults and children with persistent asthma. ICS are considered the most potent and effective long-term control treatment. ICS have been shown to reduce the symptoms of asthma severity, improve quality of life, improve lung function, prevent exacerbations, reduce healthcare utilization, and reduce the risk of death due to asthma.
2. Long-acting beta-agonists (LABA) are the preferred adjunctive therapy, when combined with an ICS, in adults and children with persistent asthma not controlled with an ICS alone. Systematic reviews and guidelines suggest the addition of LABA improve airway function, quality of life and reduce asthma symptoms and short-acting rescue inhaler use. New safety data recommends that equal consideration should be given to increasing the dose of ICS or adding a LABA in patients with uncontrolled persistent asthma. FDA labeling states that ICS/LABA combination products are indicated for patients not adequately controlled on other asthma controller medications.
3. Asthma controller medications that are alternatives, but not preferred options, for patients requiring step 2 care (persistent asthma) include: cromolyn sodium, nedocromil, montelukast, zafirlukast, zileuton and theophylline.
4. Anti-IgE therapy, i.e., omalizumab, is recommended for patients whom have a specific sensitivity to a relative allergen and require step 5 or 6 care (persistent asthma on high-dose ICS, LABA or montelukast +/- oral steroids).

Issues:

- Is there new evidence to suggest that there is a meaningful difference between asthma controller products (outcomes or safety) that would justify a change in current PDL management?

Summary of New Evidence:

In 2011 the Drug Effectiveness Review Project (DERP) released a new report on asthma controller medications comparative efficacy and safety.[2] ICS were found to be more effective (compared to LM) and safer than LABA. LABA were found to be more effective when added to ICS compared to maintaining the same ICS dose, increasing the ICS dose or when adding leukotriene receptor antagonists (LTRAs), which include montelukast and zafirlukast. The findings in the DERP are consistent with the FDA, suggesting that ICS might mitigate some of the safety risks associated with LABA treatment, however, ICS alone are still recommended as first line. This is based on evidence that combination ICS/LABA therapy compared to same dose ICS for first line therapy in adults and children with persistent asthma resulted in similar rates of exacerbations. Comparisons with higher doses of ICS resulted in fewer exacerbations compared to ICS/LABA.

There was insufficient evidence to suggest a difference in efficacy between the leukotriene modifiers (LMs), which include montelukast, zafirlukast and zileuton. However, zileuton is associated with changes in liver function tests and liver toxicity. Efficacy data offers that there may be a modest benefit to adding a LM to ICS compared to maintaining the same dose of ICS (reduced use of rescue medication but no change in exacerbations).

Several Cochrane Reviews evaluated the efficacy and safety of asthma controllers.[3-11] Studies involving LABA found an increase risk of serious adverse events and asthma-related mortality in patients not on ICS. There is insufficient data to determine the role of ICS in mitigating the risk of LABA adverse events and the effects in children. Studies using ICS/LABA combinations found adverse events to be too infrequent to draw conclusions. In efficacy studies the addition of a LABA to ICS was more effective than maintaining or increasing the dose of ICS. However, in children the addition of a LABA didn't significantly reduce the need for systemic corticosteroids and there were no significant differences in exacerbations. Adding LABA was superior to ICS on improvements in lung function. LABA was also found to be superior to LTRAs in patients inadequately controlled on ICS.

Additional studies are being required by the Food and Drug Administration (FDA) to further define the risks of severe exacerbations and death with LABA. The studies will be analyzing the effect of adding LABA/ICS combination compared to ICS alone.[12]

Conclusions:

Available evidence suggests that ICS should be offered as first line agents for patients with persistent asthma. The addition of a LABA needs to be weighed against the possible risks and should be used for patients with uncontrolled symptoms despite adequate ICS therapy. Other asthma controllers have a role in the treatment of persistent asthma but data on improved lung function and exacerbations is not as robust as for other therapies. Additional data on the safety of LABA, especially in children, is needed to help delineate the risks and benefits of treatment.

Recommendations

1. No significant new evidence is available to suggest changes in the PDL or currently available PA criteria for asthma controller medications.
2. Adopt current PA criteria with clerical changes to represent current guidelines and evidence.

Background

Long-term control medications are recommended by the National Heart Lung and Blood Institute (NHLBI) Guidelines for the Diagnosis and Management of Asthma Expert Panel Report 3 (EPR3) for the control of persistent asthma.[1] Inhaled corticosteroids are considered the most potent and effective long-term control treatment and have been documented to reduce asthma severity, improve quality of life, improve lung function, prevent exacerbations, reduce emergent health services utilization, and reduce the risk of death due to asthma. They have been shown to more effectively improve asthma control compared to any other single controller agent. Long-acting beta-agonists are recommended to be used in combination with ICS and as the preferred adjunctive therapy in those 12 years and older. However, safety issues concerning an increased risk of severe asthma exacerbations and asthma-related death with LABA therapy has prompted the FDA to advise that equal consideration should be given to increasing the dose of ICS or adding a LABA for patients not adequately controlled on ICS alone. Other asthma controllers that are not preferred but are alternatives for patients with persistent asthma (step 2 care) include: cromolyn sodium, nedocromil, luekotriene modifiers [LM (montelukast, zafirlukast, and zileuton)] and methylxanthines (i.e., theophylline). Anti-IgE therapy, i.e., omalizumab, is recommended for patients whom have a specific sensitivity to a relative allergen and require step 5 or 6 care (persistent asthma on high-dose ICS, LABA or montelukast +/- oral steroids).

DERP Update[2]:

DERP looked the comparative efficacy and safety of inhaled corticosteroids (ICS), long-acting beta-2 agonists (LABAs), leukotriene modifiers (LM), anti-IgE therapy, combination products and tiotropium in individuals with persistent asthma.

ICS:

- The report found no notable differences between the different ICS products at equipotent doses on outcomes of controlling asthma symptoms, exacerbation prevention, reduction in the need for additional rescue medication and adverse events (moderate strength of evidence).
- There was high strength of evidence that ICS monotherapy offered a greater benefit [exacerbations, rescue medication use, asthma symptoms, and quality of life (QoL)] than LM monotherapy.
- Evidence suggests that ICS and leukotriene receptor antagonists are safer than LABAs for use as monotherapy (high strength of evidence). This is based on data showing increased risk of asthma-related mortality with LABA monotherapy.
- Increasing the dose of ICS compared to adding a leukotriene receptor antagonists offered similar outcomes of efficacy and safety, as demonstrated by exacerbations, symptoms, rescue mediation use, adverse events and withdrawals due to adverse events (moderate strength of evidence).

LABA:

- There was moderate strength of evidence (in children 12 and older, insufficient for <12) that there was no difference found between formoterol and salmeterol in symptom control, exacerbations, quality of life, or harms in patients not controlled on an ICS alone. There was also no difference found between budesonide/formoterol and fluticasone/salmeterol for efficacy or harms when administered as a combination in a single inhaler (moderate strength of evidence for 12 and over, insufficient for <12).
- Indirect evidence suggests that increased risk of asthma-related death may be isolated to patients not taking an ICS.

- No evidence was available to suggest using combination ICS/LABA treatment first-line compared to ICS alone.
- Study data suggests that the addition on a LABA offers greater efficacy than a higher dose of ICS (high strength of evidence for over 12, insufficient for <12) for poorly controlled persistent asthma.
- There was high strength of evidence that greater efficacy was noted when a LABA was added compared to maintaining the same dose of ICS in patients with poorly controlled persistent asthma.
- There was high strength of evidence (over 12 years old) to support the addition of a LABA to ICS compared to adding a LTRA to ICS with similar adverse events (low strength of evidence for <12).

LM:

- There was low strength of evidence that there is no difference between montelukast and zafirlukast in decreasing rescue medication use and quality of life (insufficient evidence in <12).
- There was low strength of evidence that adding LM to an ICS improved rescue medication use compared to maintaining the same dose of ICS in adults.
- Zilueton was found to be associated with an increased risk of hepatic toxicity (1.9% vs. 0.2%, zilueton and placebo, respectively) compared to the other LM. This has resulted in requiring liver function monitoring at initiation, every month for 3 months and then every 2-3 months for the remainder of the first year

Anti-IgE Therapy:

- Omalizumab was found to be more effective than placebo for preventing exacerbations, ability to control asthma symptoms, and reduced need for rescue medication , however, it was associated with an increased number of injection site reactions and anaphylaxis.

Conclusion:

- No medication within each class was found to be more effective or harmful compared to medication within that same class.
- ICS was recommended as the initial agent for those with persistent asthma.
- The addition of a LABA is recommended for patients with poorly controlled persistent asthma already on an ICS.

<u>Cochrane Reviews:</u>

A 2011 Cochrane review looked at serious adverse events associated with salmeterol treatment[3]. Thirty-four trials were included comparing salmeterol to placebo and salbutamol. An increased risk of serious adverse events was found in studies comparing salmeterol to placebo. An increase in risk of asthma-related mortality in patients not on an ICS was found in data from two large surveillance studies. Data on asthma-related mortality in patients taking an ICS was imprecise, so no conclusion could be drawn on the ability of ICS to eliminate the increased risk associated with salmeterol. There was insufficient evidence to determine the safety effects of salmeterol in children. A similar review analyzed twenty two studies on serious adverse events in persons treated with formoterol with or without ICS. Serious adverse events were more common in formoterol groups compared to placebo but not when formoterol was compared to salbutamol or terbutaline. .[4]

Another Cochrane Review found adverse events to be too infrequent to draw safety conclusions on salmeterol and formoterol treatment (on background ICS therapy) based on four open-label studies.[5] A Cochrane Review of the combination products, salmeterol/fluticasone and formoterol/budesonide, reported asthma-related adverse events occurred infrequently and there were no asthma-related deaths. Adverse event rates were similar between the treatments.[6]

Four Cochrane Reviews examined the effect of adding a LABA to ICS in various scenarios in adults and children with asthma. The addition of LABA to ICS as a first line treatment in patients whom had persistent asthma and were steroid-naïve compared to ICS alone, resulted in no significant difference in the need for oral steroid treatment for exacerbations between the two therapies. However, the LABA and ICS combination resulted in improvements in FEV1, symptoms and reduced rescue beta2-agoinst use compared to ICS with similar rates of adverse events. In a second comparison, as first line treatment, the LABA/ICS combination was associated with a greater risk for needing oral steroids compared to a higher dose of ICS alone.[7] An other review looked at adding a LABA to ICS compared to continuing the same dose of ICS in adults and children. The addition of LABA to ICS was found to reduce the need for oral steroid therapy, improve FEV1, and slightly decrease the need for rescue beta2-agonists. The differences in serious adverse events were similar between groups.[8] An updated review from 2008 analyzed the addition of a LABA to ICS compared to a higher dose of ICS in adults and children with moderate persistent asthma. Unlike the previous review, this review found that the addition of a LABA to ICS was more effective in reducing the risk of exacerbations in adolescents and adults as well as improving lung function, symptoms, beta2-agonist rescue use and fewer withdrawals due to poor asthma control. In children the addition of a LABA to ICS was associated with a trend toward an increased risk of exacerbations requiring oral steroids and hospitalizations compared to an increased dose of ICS.[9] An additional review looked just at children and the effect of adding LABA to ICS compared with the same or increased dose of ICS. Adding a LABA to ICS did not significantly reduce the need for systemic corticosteroids but was superior to maintaining the ICS dose on improving lung function. When a higher ICS dose was used there was no significant difference found in exacerbations compared to adding a LABA to ICS.[10]

A Cochrane review of 17 randomized, controlled trials in patients with chronic asthma compared the addition of a LABA versus anti-leukotrienes (LTRA) to ICS therapy. The addition of LABA to ICS resulted in a lower number of patients requiring oral steroids compared to the addition of a LTRA with a number needed to treat (NNT) of 38 (95% CI 22 to 244) to prevent one exacerbation over 48 weeks by adding a LABA compared to a LTRA. The addition of a LABA was found to be associated with more severe adverse events compared to LTRAs (RR 1.35, 95% CI 1.00 to 1.82). Overall, the addition of a LABA was superior to LTRAs in patients inadequately controlled on ICS, however, there was insufficient evidence in children to make a recommendation.[11]

Overall, the Cochrane reviews found that that addition of LABA/ICS was the same or better than ICS (same dose or increased dose) in adults with persistent asthma. In children, adding LABA/ICS compared to the same or higher dose ICS resulted in mixed results with a trend toward an increased risk in exacerbation in the LABA/ICS group. However, another review found no significant difference in exacerbations between the groups. LABA monotherapy was found to be associated with increased asthma-related mortality and serious adverse effects. The rate of adverse effects were too low to determine if background ICS negates this risk.

FDA Warnings[12]:

LABA:

- 4/2011: The FDA is requiring the manufacturers of LABAs to conduct five randomized, double-blind, controlled clinical trials comparing the addition of LABAs to ICS versus ICS alone. The recommendation is to further evaluate the safety of LABAs. Four trials will be conducted in persons with asthma 12 and older and one trial in pediatric patients 4-11 years old. Results are expected in 2017.
- 6/2010: The FDA requires updated recommendations for using LABA to be added to drug labels. Labels must warn patients of increased risk of severe exacerbations of asthma symptoms and possibly death.
- New recommendations state:
    - Use of LABA alone or without use of long-term asthma control medication, such as an ICS, is contraindicated (absolutely advised against) in the treatment of asthma.
    - LABAs should not be used in patients whose asthma is adequately controlled on low or medium dose ICS.
    - LABAs should only be used as additional therapy for patients with asthma who are currently taking but are not adequately controlled on a long-term asthma control medication, such as inhaled corticosteroid.
    - Once asthma control is achieved and maintained, patients should be assessed at regular intervals and step down therapy should begin (e.g., discontinue LABA), if possible without loss of asthma control, and the patient should continue to be treated with long-term asthma control medication, such as an inhaled corticosteroid.
    - Pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should use a combination product containing both an ICS and a LABA, to ensure adherence with both medications.

Other Literature:

- Salpeter provided an updated analysis on the safety of long-acting beta-agonists in patients using ICS. A previous meta-analysis by Salpeter found LABA was associated with an increased risk of exacerbations requiring hospitalizations and an increase in life-threatening exacerbations. In this recent analysis of pooled trial data , catastrophic asthma events (asthma-related intubation or death) were increased four times the amount with LABA and ICS compared to ICS alone (OR 3.7, 95% CI 1.4 to 9.6).[12]

Appendix 1: PA CRITERIA

# Asthma Controller Drugs

**Goal(s):**

- *The purpose of this prior authorization policy is to ensure that non-preferred asthma controller drugs are used for an above the line indication.*

**Initiative:** Asthma Controller PDL

**Length of Authorization: up to 12 months**

**Requires PA :**
- Non-preferred drugs

**Covered alternatives:**
See PDL list at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

| Approval Criteria | | |
|---|---|---|
| **1.** Is the requested drug montelukast (Singulair®)? | Yes: Go to Leukotriene Inhibitor Criteria | No: Go to #2 |
| **2.** Is the request for a LABA/ICS combination product? | Yes: Go to LABA/ICS criteria | No: Go to #3 |
| ***3.*** What is the diagnosis being treated? | Record ICD-9 Code | |
| **4.** Is this an OHP covered diagnosis? | Yes: Go to #5 | NO: PASS TO RPH<br>DENY (not covered by OHP) |
| **5**.Is this a continuation of current therapy (i.e. filled prescription within prior 90 days)?<br>Verify via pharmacy claims. | Yes: Document prior therapy in PA record. Approve for 1 year. | No: Go to #6 |
| **6**. Will the provider consider a change to a preferred product?<br><br>Message:<br>- Preferred products do not require a PA<br>- Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee. | Yes: Inform provider of covered alternatives | No: Approve for 1 year or length of prescription, whichever is less. |

# LABA/ICS Inhalers

**Goal(s):**

- *Approve LABA/ICS only for covered diagnosis (e.g. COPD or Asthma and on concurrent controller medication)*
- *LABA are only indicated for use in clients with Asthma already receiving treatment with an asthma controller medication (e.g. Inhaled corticosteroids or leukotriene receptor antagonists).*

**Initiative: LABA/ICS Step Therapy**

**Length of Authorization: 6 months - 1 year**

**Covered alternatives that DO NOT require a PA:**
**See PDL list at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml**

**Step Therapy Required prior to coverage:**

Asthma: oral corticosteroid inhalers (see preferred drug list options at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml),

COPD: short and long-acting beta-agonist inhalers, anticholinergics and inhaled corticosteroids (see preferred drug list options at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml),DO NOT require prior authorization.

**Requires PA**: All combination inhaled corticosteroid/long-acting beta-agonist inhalers.

| **Approval Criteria** | | |
|---|---|---|
| 1. Does patient have asthma or reactive airway disease (ICD-9: 493, 493.0-493.93)? | **Yes:** Go to **2** | **No:** Go to **3** |
| 3. Has patient:<br>• failed an inhaled corticosteroid or other controller medication OR<br>• Had ≥2 exacerbations requiring oral systemic corticosteroids in the past year, OR<br>• Is there documentation of step 3 or higher asthma OR<br>• Is there a hospital admission or ER visit related to asthma or reactive airway disease within last 60 days? | **Yes**: Document the following:<br>Date of trial, drug, reason(s) for failure or contraindications OR chart notes of asthma severity in the PA record<br><br>Approve for 1 year if this is patient's first prescription for a combination inhaler or if this is a continuation of therapy and patient is well controlled on current dose. | **No**: **PASS TO RPH DENY (Medical Appropriateness).** |
| **3.** Does patient have COPD (ICD-9 496) or Chronic bronchitis (491.1-2.) and/or emphysema (492.xx)?? | **Yes:** Go to **4** | **NO: PASS TO RPH DENY (Medical Appropriateness).**<br>*Need a supporting diagnosis.* |

| | | |
|---|---|---|
| | | *If prescriber believes diagnosis appropriate inform them of the provider reconsideration process for Medical Director Review.* |
| **4**. Has patient failed a combination of **short acting** (ipratroprium or ipratroprium/albuterol) **and long-acting** (salmeterol, formoterol and/or tioptropium) inhaled bronchodilators? | **Yes:** Document the following: Date of trial, drug, reason(s) for failure or contraindications in the PA record**.** Approve for 1 year if this is patient's first prescription for a combination inhaler or if this is a continuation of therapy and patient is well controlled on current dose. | (**No:** Pass to RPH; Deny, (Medical Appropriateness). *Gold guidelines recommend addition of inhaled corticosteroid if disease severity persistent despite use of combination of short acting and long-acting bronchodilators. http://www.goldcopd.org/uploads/users/files/GOLDReport_April112011.pdf* |

# Leukotriene Inhibitors

**Goals:**

- Approve motelukast only for covered diagnosis.
- Allergic rhinitis treatment is covered by the OHP only when complicated by other diagnoses (e.g. asthma, sleep apnea).
- Promote use that is consistent with medical evidence**.**

**Length of Authorization: 6 months or 2 years (diagnosis specific)**

**Covered Alternatives:**

- Preferred alternatives listed at: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml
- Allergic Rhinitis: cetirizine, chlorpheniramine, diphenhydramine, loratidine, and hydroxyzine DO NOT require prior authorization.
- Asthma: Oral corticosteroid inhalers and zafirlukast (Accolate®) DO NOT require a prior authorization.

**Requires PA:**

- Non-preferred drugs
- Montelukast (Singulair ®)

| Approval Criteria | | |
|---|---|---|
| 1. What is the diagnosis being treated? | Record ICD-9 | |
| 2. Does the client have asthma or reactive airway disease (ICD-9:493.xx)? | Yes: Approve for 2 years | No: Go to #3 |
| 3. Does the client have a diagnosis of allergic rhinitis, allergic conjunctivitis, or chronic rhinitis/pharyngitis/nasopharngitis? (ICD-9: 472.xx, 372.01-05, 372.14, 372.54, 372.56, 477.xx, 995.3, Vo7.1) | Yes: Go to #4 | No: Go to #6 |
| 4. Does the client have other co-morbid conditions or complications that are above the line?<br>- Acute or chronic inflammation of the orbit (376.0-376.12)<br>- Chronic sinusitis (473.xx)<br>- Acute sinusitis (461.xx)<br>- Sleep apnea (327.20, 327.21, 327.23-327.29, 780.51, 780.53, 780.57)<br>- Wegener's Granulomatosis (ICD-9: 446.4) | Yes: Go to #5 | No:Pass to RPH; Deny (Not covered by the OHP) |
| 5. Does the client have contraindications (e.g.pregnant) or had insufficient response to at least 2 alternatives? Document | Yes: Approve for 6 months | No: Pass to RHP; Deny (Cost-Effectiveness) |
| 6. Is the diagnosis COPD (496) or Obstructive Chronic Bronchitis? (491.1-491.2) | Yes: Pass to RPH; Deny (Medical appropriateness, leukotrienes not indicated) | No: Pass to RPH; Go to #7 |
| 7. Is the diagnosis Chronic Bronchitis? (491.0, 491.8, 491.9) | Yes: Pass to RPH; Deny (Not covered by OHP) | No: Pass to RPH, Go to #8 |

| | | |
|---|---|---|
| 8. RPH only: Is the diagnosis above the line or below the line? | Above: Deny with yesterday's date (medically appropriateness)<br><br>Use clinical judgment to approve for 1 month starting today to allow for time to appeal.<br><br>Message: "Although the request has been denied for long term use because it is considered medically inappropriate, it has also been approved for one month to allow time to appeal." | Below: Deny, (Not covered by the OHP) Message: "The treatment for you condition is not a covered service on the Oregon Health Plan"<br><br>(e.g. URI-465.9 or uticaria -708.0, 708.1, 708.5, 708.8, 995.7 should be denied) |


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