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Abbreviated Class Review: Chronic Obstructive Pulmonary Disease (COPD)

Executive summary:

Month/Year of Review: February 2012

New Product for review:	**Manufacturer:**	**Dossier received:**
Indacaterol (Arcapta®)	Novartis Pharmaceuticals	No
Roflumilast (Daliresp®)	Forest Pharmaceuticals	Yes

Available Alternatives

Current Preferred Agents:		**Requires PA***
Pulmonary Anticholinergic Inhalers	**Long-acting Controllers**	Advair (fluticasone/salmeterol)
Ipratropium (Atrovent HFA®)	Flunisolide (Aerobid®)	Symbicort (budesonide/formoterol)
Ipratropium/Albuterol AER (Combivent®)	Mometasone (Asmanex®)	Dulera (mometasone/formoterol)
Ipratropium Bromide Solution	Fluticasone (Flovent Diskus®)	
Ipratropium-Albuterol AMPUL-NEB	Fluticasone (Flovent HFA®)	
Tiotropium (Spiriva®)	Formoterol (Foradil®)	
	Budesonide (Pulmicort Flexhaler®)	
	Beclomethasone (Qvar®)	
	Salmeterol (Serevent Diskus®)	

*Requires fail of combination of short acting and long-acting inhaled bronchodilators (Appendix 1)

Previous Conclusions:

Beta$_2$Agonists (HRC 2007):

1. There is no significant difference between salmeterol and formoterol in COPD patients in efficacy or effectiveness for respiratory symptoms in the outpatient setting.

2. There is no evidence of comparative difference in efficacy or effectiveness among the short-acting inhaled beta$_2$-agonists in the outpatient setting
3. There is insufficient evidence to determine comparative differences in safety or rates of adverse events among inhaled long acting beta$_2$-agonists, when used in COPD patients in the outpatient setting.

Inhaled Corticosteroids (HRC 2006):

1. There is insufficient evidence to evaluate difference among ICSs for comparative effectiveness.
2. There is consistent evidence that ICSs do not reduce mortality or improve quality of life in COPD.

Inhaled Anticholinergics: (Provider Synergies 2010)

1. Both agents in this class (ipratropium and tiotropium) have been shown to improve bronchodilation, dyspnea, exacerbation rates, and health-related quality of life
2. Adverse effects are limited primarily to dry mouth that appears to resolve with continued use.

Reason for Review:

Two new FDA approved medications indicated for the treatment of COPD are now available. Indacaterol (Arcapta®) is the first LABA available that is dosed once daily.[1] It is available as a single drug inhaled product and is indicated for COPD only. Roflumilast (Daliresp®) is the first oral phosphodiesterase-4 (PDE4) inhibitor made available in the U.S.[2] It has a novel mechanism of action and is indicated for a very narrow COPD population to help reduce the risk of exacerbations. Refer to individual drug reviews for efficacy and safety evaluations which can be found on the Oregon Pharmacy and Therapeutics website: http://pharmacy.oregonstate.edu/drug_policy/meetings.

Additionally, there has been several new or revised COPD treatment guidelines published. The National Institute for Clinical Excellence in the United Kingdom (NICE) and the international Global Initiative for Chronic Obstructive Lung Disease (GOLD) updated their respective guidelines in 2010. An international collective of physician groups: the American College of Physicians (ACA), the American College of Chest Physicians (ACCA), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) also published COPD treatment recommendations in 2011.[3, 4, 5]

Several high quality systematic reviews have been published in the interim as well. The Canadian Agency for Drugs and Technologies in Health (CADTH) evaluated the effectiveness of triple therapy (ICS + LABA + LAMA) compared with dual (ICS + LABA) or monotherapy (LAMA) for moderate-to-severe COPD in 2010.[6] The Cochrane group has numerous reviews on COPD treatment that have become available in 2010 and 2011. These systematic reviews compared the effectiveness of the various COPD classes, many looking at whether combination therapy has benefits over monotherapy.[7, 8, 9, 10, 11]

Issues:

- Is there new comparative evidence that there is a meaningful difference in LABAs, LAMAs, and ICSs or combinations thereof in long term clinical outcomes or safety that could justify changes in current PDL management?
- Is there any evidence that indacaterol or roflumilast are more effective or safer than currently available medications?

Summary:

Three organizations recently updated their evidence based treatment guidelines for management of stable COPD.[2,3,4] These include starting treatment with a long-acting bronchodilator in patients with moderate stage COPD (FEV_1>50%) experiencing dyspnea symptoms. Addition of an ICS is not recommended until more severe disease (stage $\geq$ 3; repeated exacerbations) presents. All guidelines treat progressing COPD disease in the same stepwise fashion: short-acting bronchodilator, long-acting bronchodilator, additional long-acting product(s)-LABA, LAMA, or ICS, and finally long-term O_2 therapy. None of the current guidelines can conclude that there is a meaningful difference or favor individual products within each class.[2, 3, 4]

The guidelines differ in where they put emphasis on one long-acting class over another. NICE favors LAMA over LABA for monotherapy in more severe disease. Both GOLD and the joint CHEST guidelines consider LABA and LAMA as therapeutically equivalent. NICE and GOLD favor ICS products for patients with more severe disease, while the joint CHEST guideline offers a weak recommendation for ICS products in this population.[2,3,4]

The role of combination therapy is not yet entirely established. In the last two years, the Canadian Agency for Drugs and Technologies in Health (CADTH) and the Cochrane Collaboration have published systematic reviews attempting to clarify the issue of what combination might be the most efficacious. Two Cochrane reviews updated in 2010 compared combination dual ICS + LABA therapy with ICS or LABA monotherapy. One concluded adding an ICS to LABA monotherapy decreased exacerbation but increased pneumonia rates, while LABA therapy alone showed modest improvements in lung function.[7] The other 2010 Cochrane review examined LABA/ICS combination therapy versus ICS monotherapy and found all outcomes, including mortality, exacerbations, and hospitalizations, improved with combination therapy.[8]

Several other reviews looked at triple therapy (LAMA + LABA + ICS) versus LAMA monotherapy or dual therapy with either an ICS + LABA or LAMA + LABA combination.[6, 9, 10] There was some evidence for improvement in lung function and quality of life measures with triple therapy; however, no conclusions as to whether triple therapy improved mortality or hospitalizations could be made. These reviews are severely limited by the lack of clinical trials examining triple therapy. Inadequate data also hampered a Cochrane review looking at LAMA monotherapy compared with ICS/LABA combination therapy; the authors drew no conclusions due to insufficient evidence.[11] In the recent clinical trial POET-COPD, LAMA monotherapy was shown to be superior to LABA monotherapy; decreasing total annual exacerbation rate by 11% (0.64 vs. 0.72, RR 0.89 95% CI 0.83 to 0.96). Although more evidence is needed, LAMA monotherapy may be more effective at improving symptoms and decreasing exacerbations than LABA monotherapy in patients initiating treatment, especially with more severe disease. [12]

Entering the COPD landscape are two new medications. The first, indacaterol (Arcapta®), is a new LABA. Unlike the currently available LABAs, indacaterol is dosed one daily and is not available in combination with an ICS entity. In clinical trials, indacaterol was shown to improve lung function and improve symptom control compared with placebo.[13, 14, 15, 16, 17] The approved dose, however, was not compared with available LABAs or LAMAs, making it difficult to establish clinical efficacy. The second is roflumilast (Daliresp®), a selective phosphodiesterase-4 inhibitor. Roflumilast is not used to control symptoms; it is indicated to decrease the risk of exacerbations in patients with severe COPD who have chronic bronchitis and a history of exacerbations. In clinical trials when compared to placebo, it decreased exacerbation rates only in the specific indicated population. Several adverse events not seen with other COPD medications (weight loss, suicide ideation, depression) were significantly higher in roflumilast versus placebo groups.[18, 19, 20]

Conclusions:

Guideline recommendations are similar although not uniform. GOLD, NICE and CHEST guidelines agree in treating COPD patients in a stepwise fashion, starting with long-acting bronchodilator monotherapy and adding agents with disease progression. GOLD and CHEST make no differentiation between the long-acting bronchodilator classes LABA and LAMA, while NICE recommends initiating with LAMA therapy in COPD patients with more severe symptoms. All three guidelines recommend adding an ICS only when warranted by symptoms and disease severity (stage 3; exacerbations). None of the guidelines make recommendations regarding triple therapy use.

The CADTH and Cochrane systematic review conclusions confirm the guideline recommendations. A LABA product is recommended in COPD patients with less severe symptoms as an initial agent, while a LAMA product may be a better first line choice for a patient with more severe disease. Addition of an ICS is recommended for patients still experiencing symptoms and persistent exacerbations with monotherapy. There is limited evidence for the advantage of triple therapy in outcomes important to COPD: exacerbation, pneumonia, hospitalization and mortality rates. More evidence is needed to establish if triple therapy brings any additional benefit.

Remaining Issues:

There is still little comparative evidence for long-term benefits or harms of LABAs, LAMAs, and ICSs. The debate as to which class, or combination of classes, is best remains unresolved. More comparative effectiveness research for triple therapy versus dual therapy is needed.

Further comparative studies are needed to evaluate:

- Comparisons of triple therapy with various combinations of dual and monotherapy
- Outcomes over several years to compare pneumonia, hospitalization and mortality rates

Recommendations:

1. No significant comparative effectiveness evidence exists since last OHA class review necessitating PDL changes. Recommend comparing costs of agents for any further additions or eliminations to preferred products.
2. Due to limited long term effectiveness or safety evidence compared to multiple alternatives, recommended making indacaterol a nonpreferred LABA.
3. Recommend maintaining roflumilast as a non-preferred agent and include the following clinical criteria necessary for approval to ensure it is only used in the appropriate patient population:
    a. Patient has severe or very severe COPD with chronic bronchitis and frequent exacerbation.
    b. Patient has documented failure with an ICS or ICS combination product or tiotropium
    c. Patient is on a concurrent long acting controller medication (LABA or LAMA) as monotherapy or in combination with other therapies.

Background/Current Landscape

COPD is the fourth leading cause of morbidity and mortality in the United States. More than 13 million US adults have COPD and in 2010, the cost to the nation for COPD was over 45 billion.[21] COPD is a condition characterized by limitation of airflow that is not fully reversible. Airflow limitation is usually progressive and associated with abnormal inflammatory response. It is caused by a mixture of small airway disease (chronic bronchitis) and parenchymal destruction (emphysema). Risk factors can include non-modifiable and modifiable causes. The leading predictor of COPD is a history of long term cigarette smoking. [3, 4, 5]

Current guidelines consider spirometry the gold standard in diagnosing COPD. [3, 4, 5] Spirometry is described as the most reproducible, standardized, and objective way of measuring airflow limitation.[22] Airflow limitation that is not fully reversible is defined as present when the post-bronchodilator ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) is below 0.70. [3, 4, 5] All patients with COPD, regardless of disease severity, have an FEV_1/FVC ratio of <0.70. Disease severity, however, is evaluated by the patient's FEV_1 measured against a population standard. Using spirometry, COPD patients are classified into four stages: Stage I (mild): $FEV_1 \geq 80$ % predicted, Stage II (moderate): 80 % > FEV_1 > 50 % predicted, Stage III (Severe): 50 % > FEV_1 > 30 % predicted, and Stage IV (Very severe): $FEV_1 < 30$ % predicted. Exacerbations and symptoms (i.e. SOB, cough, and sputum production) tend to increase with disease progression. [3, 4, 5]

Long-acting bronchodilators are used to improve breathing in adults with airflow obstruction due to COPD including chronic bronchitis and emphysema. Two types of bronchodilators, long-acting beta-2 agonists (LABA) and long-acting muscarinic antagonists (LAMA), are indicated as maintenance therapy for COPD patients stage 2 or higher. LABAs are considered a mainstay of COPD therapy, and are often the starting maintenance

medication for a patient. Current treatment guidelines recommend LABAs as a central therapy for the alleviation of symptoms and are recommended for treatment of COPD. [3, 4, 5] However, recent evidence suggests initiating a LAMA instead of a LABA in patients with more severe symptoms may improve outcomes such as hospitalizations and mortality.[12] Inhaled corticosteroids (ICS) are not used as an initial therapy but added in patients with more severe symptomatic COPD (stage 3; exacerbations).[3, 4, 5]

None of the existing COPD classes have been shown to modify long term decline in lung function[4] and reduction of therapy once symptoms are controlled is not always possible. Further deterioration of lung function frequently entails the progressive introduction of more medications. All three classes are used frequently in combinations of dual and triple therapy; and combination products of LABAs and ICS are available and intended to facilitate adherence to medication. When to use combination therapy instead of monotherapy has not clearly been established. Triple therapy is not uncommon and is even more controversial. At this time, there is insufficient evidence to show triple therapy improves exacerbation, hospitalization or mortality rates.[6, 9, 10]

National/International Guidelines

1. Diagnosis and management of stable COPD : a clinical practice guideline update[3]

Developer:
American College of Physicians, American Thoracic Society,
European Respiratory Society, American College of Chest Physicians

Published:
CHEST, August 2011

Recommendations:

1. There is moderate-quality evidence that asymptomatic COPD patients staged moderate or better (stages 1 &2; >50% FEV) should receive no treatment.
2. Based on a weak recommendation and low-quality evidence, symptomatic patients with an FEV_1 between 60-80% may begin treatment with inhaled bronchodilator (LABA or LAMA).
3. There is moderate-quality evidence that symptomatic patients with an FEV_1<60% should begin treatment with an inhaled bronchodilator (LABA or LAMA).
4. There is moderate-quality evidence that monotherapy can begin with either a LABA or LAMA. Evidence shows no significant difference in outcomes among various monotherapies.

5. There is moderate-quality evidence and a weak recommendation that combination therapy may be utilized for symptomatic patients with an $FEV_1 < 60\%$. The evidence is still insufficient to support a strong recommendation for the broad use of combination therapy.

Critique:
These evidence based guidelines utilized strong methods performed by the Minnesota Evidence-based Practice Center including a literature search, internal peer review, and individual quality assessment of trials included. It was intended for physician use and focused on clinically important outcomes of exacerbations, mortality, hospitalizations, and quality of life. This guideline is funded by the American College of Physicians, a professional organization dedicated to the practice of internal medicine[24].

2. **Global Strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease[4]**

Developer:
Global Initiaitve for COPD
National, Heart, Lung, and Blood Institute
World Health Organization

Published:
2010 (revision)

Recommendations:
1. There is high-quality evidence that patients with moderate COPD ($FEV_1 \geq 50\%$) who experience dyspnea should start treatment with a long acting inhaled bronchodilator. There is insufficient evidence to favor one long-acting bronchodilator over others.
2. There is moderate-quality evidence that in patients with severe ($FEV_1 < 50\%$) to very severe COPD who experience repeated exacerbations, the addition of an ICS reduces the frequency of exacerbations and improves health status.

Critique:
Global Initiative from Chronic Lung Disease (GOLD) guideline for COPD provides a more detailed overview than most other guidelines and includes aspects outside of management and treatment of stable COPD including acute, emergency and preventive care, as well as treatment of co-morbidities common in the COPD population. The target audiences for this guideline are healthcare providers in the primary care setting. A detailed search strategy was conducted, and a defined rating scheme for rating the strength of the evidence is also used. Evidence is ranked as "A, B, C or D" on the basis of the source of the data.
GOLD is funded by a mixture of private non-profit and for-profit companies. Numerous pharmaceutical companies are contributors including AstraZeneca (Pulmicort™), Novartis (Foradil™), GlaxoSmithKline (Advair™), and Pfizer (Spiriva™).

3. **Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care**[5]

Developer:
National Institute for Health and Clinical Excellence

Published:
2010 (updated)

Recommendations:

1. There is moderate-quality evidence that patients experiencing "exacerbations and persistent breathlessness" and have an $FEV_1 \geq 50\%$ should be treated with a long-acting beta-2 agonist (LABA) or a long-acting muscarinic agonist (LAMA) monotherapy.
2. There is moderate-quality evidence that patients experiencing "exacerbations and persistent breathlessness" and have an $FEV_1 < 50\%$, should be treated with a LAMA as monotherapy or with dual therapy of an inhaled corticosteroid (ICS) & LABA or LABA-LAMA combination.
3. There is low-to-moderate-quality evidence that patients with persistent exacerbations should be treated with dual or triple therapy: an ICS-LABA or ICS-LABA-LAMA combination.

Critique:
Unlike the two previous guidelines, the NICE COPD guideline is aimed at a much larger target audience and is broader in scope.
Search criteria are given in broad descriptions, but with direction to appendices with more detailed information. Internal and external peer reviews were conducted to validate the guideline. A hierarchy of Evidence Rating system was used to assess the quality and strength of the evidence
This guideline is funded by the Government of the United Kingdom.

Systematic reviews:

Triple Therapy for Moderate to Severe Chronic COPD[6]
CADTH

Published in December 2010
This systematic review evaluated the clinical efficacy of single, dual (ICS + LABA) and triple (ICS + LABA + LAMA) therapy in patients with COPD. Clinical outcomes of interest were lung function, hospitalizations, exacerbations, and quality of life. CADTH also assessed cost-effectiveness and impact on Canadian Health systems. The review included only tiotropium as the monotherapy comparator. Studies included were not designed to analyze efficacy in triple versus dual therapy. The evidence is extremely limited in this review and based on only four studies evaluating triple therapy and can only be generalized to patients with moderate-to-severe COPD with a history of exacerbations and smoking.

Conclusions:

- There is limited evidence of moderate quality that triple therapy, dual therapy, and combination therapy decreased the number of COPD hospitalizations, improved lung function, and quality of life in patients with moderate to severe COPD in comparison with tiotropium monotherapy.
- There is insufficient evidence to determine if triple therapy is clinically superior to dual bronchodilator therapy or combination therapy.

***Cochrane Collaboration**:*

1. "Combination inhaled steroid and long-acting beta2-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease"[9]

Published 2011
The main objective was to examine the efficacy of triple therapy (LABA + tiotropium + ICS) versus LAMA monotherapy or dual therapy (LABA + ICS). Clinical outcomes of interest included lung function, hospitalizations, mortality, and quality of life. Only three trials met the inclusion criteria for the review, limiting the external validity of the review.

Conclusions:
- There is weak evidence that triple therapy improved lung function and quality of life in patients COPD in comparison with dual therapy.
- There is insufficient evidence as to whether triple therapy has additional benefits in decreasing mortality, hospitalizations, exacerbations and pneumonia.

2. "Combination inhaled steroid and long-acting beta2-agonist versus tiotropium for chronic obstructive pulmonary disease"[11]

Published 2011
This systematic review looked at the relative effects of LAMA monotherapy versus LABA +ICS combination therapy. Clinical outcomes of interest included exacerbations, hospitalizations, and mortality. Again only three trials met the review's inclusion criteria. In the largest study included, there were serious issues surrounding withdrawals calling into question the validity of the study.

Conclusions:
- There is insufficient evidence to compare efficacy and safety of LAMA monotherapy with LABA+ICS dual therapy

3. "The effect of adding inhaled corticosteroids to tiotropium and long-acting beta2-agonists for chronic obstructive pulmonary disease"[10]

Published 2011
This systematic review examined if there is additional efficacy in adding an ICS to LABA + LAMA dual therapy with dual LABA+LAMA therapy alone. Only one trial met the review's inclusion process and that study had some high, uneven rates of attrition.

Conclusions:

- There is insufficient evidence to conclude if triple combination therapy has greater efficacy over LABA/LAMA dual therapy.

4. "Combined corticosteroid and long-acting beta-agonist in one inhaler versus inhaled steroids for chronic obstructive pulmonary disease"[8]

Published 2010
This systematic review examined whether combination LABA/ICS therapy provided any additional benefit over ICS monotherapy. Clinical outcomes of interest included lung function, exacerbations, hospitalizations, mortality, and quality of life. This review included seven studies with a fairly homogenous population of severe COPD patients. The review also looked at differences between the two combination products available for COPD: salmeterol/fluticasone and formoterol/budesonide.

Conclusions:

- There is strong evidence combination LABA/ICS therapy reduces mortality compared with ICS monotherapy.
- There is strong evidence combination therapy reduces hospitalizations and exacerbations compared with ICS monotherapy.
- There is strong evidence of greater improvements in lung function and quality of life measures with combination therapy versus ICS monotherapy.
- There is strong evidence that adverse events are similar between combination and monotherapy populations.
- There is insufficient evidence to determine if one combination product is superior to the other.

5. "Combined corticosteroid and long-acting beta-agonist in one inhaler versus long-acting beta-agonists for chronic obstructive pulmonary disease"[7]

Published 2010
The objective of this systematic review is to assess the effectiveness of combination LABA/ICS therapy compared with LABA therapy alone. Clinical outcomes of interest were exacerbations, mortality, and pneumonia. Ten studies were included in this review. The majority of studies used salmeterol/fluticasone as the combination product.

Conclusions:

- There is strong quality evidence that combination dual therapy (LABA+ICS) reduces exacerbations compared with LABA monotherapy.
- There is insufficient evidence combination therapy reduces mortality or hospitalizations compared with LABA monotherapy.
- There is strong evidence of greater risk of developing pneumonia with combination therapy versus LABA monotherapy.

Appendix 1
Current PA Criteria

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).*
- *Promote use that is consistent with Oregon Asthma Guidelines and medical evidence. http://www.oregon.gov/DHS/ph/asthma/pubs.shtml#oregon*

Iniative: 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 (Atrovent, Combivent), inhaled corticosteroids (see preferred drug list options at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml), and theophylline DO NOT require prior authorization.

Requires PA: Advair diskus and Advair HFA (fluticasone/salmeterol) HICL= 19963, Symbicort (budesonide/formoterol) HICL= 21993, Dulera (mometasone/formoterol) HICL = 37050

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**
2. Has patient: • failed an inhaled corticosteroid or other controller medication OR • Is there documentation of step 3 or 4 asthma OR • Is there a hospital admission or ER visit related to asthma or reactive airway	**Yes**: Document the following: Date of trial, drug, reason(s) for failure or contraindications OR chart notes of asthma severity in the PA record	**No**: **PASS TO RPH** **DENY (Medical Appropriateness).** *Oregon Asthma guidelines*

disease within last 60 days?	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.	*recommend combination inhaled corticosteroids plus LABA after failure of low or medium dose ICS. http://www.oregon.gov/DHS/ph/asthma/pubs.shtml#Oregon_Guiding_Documents_for_Asthma*
3. Does patient have COPD (ICD-9 496) or Chronic bronchitis (491.1-2.)?	**Yes:** Go to **4**	**NO: PASS TO RPH DENY (Medical Appropriateness).** *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*

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