



Via Hand Delivery

January 19, 2007

Leslie V. Norwalk, Esq.
Acting Administrator
Centers for Medicare & Medicaid Services
U.S. Department of Health and Human Services
Room 445-G, Hubert H. Humphrey Building
200 Independence Avenue, SW
Washington, DC 20201
<http://www.cms.hhs.gov/eRulemaking>

Re: National Coverage Analysis for Nebulized Beta Adrenergic Therapy for Lung Diseases (CAG - 00354N)

Dear Ms. Norwalk:

The American Association for Homecare (AAHomecare) submits the following comments on the Centers for Medicare and Medicaid Services' (CMS') national coverage analysis (NCA) for nebulized beta adrenergic agonist therapy for lung disease. AAHomecare is the only national association representing every line of service within the homecare community. AAHomecare members include home health agencies and suppliers and manufacturers of DME, prosthetics, orthotics, and supplies (collectively "DMEPOS"), rehab and assistive technologies, and pharmacies that provide infusion and inhalation drug therapies to patients in their homes. Our membership reflects a cross-section of the homecare community, including national, regional, and local providers and suppliers. AAHomecare and its members are committed to advancing the value and practice of quality health care services at home.

I. BACKGROUND

As you are aware, coverage for outpatient drugs under Medicare Part B is limited to a very small number of drugs. With respect to respiratory medications, Medicare covered inhalation drugs used with a nebulizer under the premise that the drug was a supply necessary to accomplish the therapeutic objective of the nebulizer.¹ Medicare pays for the nebulizer, the drug, and any necessary supplies. Inhalation drugs differ significantly from other outpatient drugs that are self-administered because they require an array of professional and administrative services, including delivery, education, oversight, and monitoring to ensure that the drug therapy is administered safely and effectively in the home.

In March 2006, the program safeguard contractors (PSCs) for the durable medical equipment regional contractors (DMERCs) initiated a revision to the local coverage determination

(LCD) for nebulizers. The revised LCD would make payment and coverage changes for a number of respiratory drugs including levalbuterol. Specifically, the PSCs proposed that Medicare should pay no more for levalbuterol than the allowance established for albuterol.

Before the DMERC PSCs published a final nebulizer LCD, CMS published the above referenced NCA, requesting public comments on the use of nebulized beta adrenergic agonist therapy for individuals with lung disease generally, and in particular, the use of levalbuterol in the Medicare population with chronic obstructive pulmonary disease (COPD). AAHomecare members with clinical expertise in respiratory care reviewed the relevant science and concluded that the studies, as a whole, demonstrate that the use of nebulized beta agonists, including levalbuterol, is both reasonable and necessary for use in the treatment of individuals with COPD. Finally, given the potential that a final nebulizer LCD, if issued prematurely, could conflict with a national coverage determination (NCD), the LCD should be withdrawn, or at least held in abeyance pending the issuance of an NCD by CMS.

II. COMMENTS

A. Chronic Obstructive Pulmonary Disease is a Chronic, Progressive and Debilitating Disease

COPD is the leading cause of morbidity and mortality worldwide.² Approximately 15 million Americans have been diagnosed with COPD, and an estimated 15 million more have undiagnosed COPD. COPD costs the U.S. economy over \$18 billion a year in direct medical costs and an estimated \$11 billion in indirect costs.³ COPD is responsible for a significant part of all physician office visits and emergency room (ER) visits and ranks number three (3) in acute hospital admissions among Medicare aged persons. Based on 2001 data from Medicare, more than 397,000 patients were discharged from acute care hospitals with a diagnosis of COPD. The average length of stay for a COPD admission is 5.1 days at the rate of \$4,000 per day. Medicare payments to hospitals for routine COPD admissions alone exceed \$1.5 billion.

COPD includes chronic bronchitis and emphysema and has been defined recently as the physiologic finding of nonreversible pulmonary function impairment.⁴ COPD is the fourth leading cause of death in the world and the only leading cause of death for which both prevalence and mortality are rising.⁵ COPD is a disease characterized by severe airflow limitation resulting from chronic inflammation of the airways, decrease in functional lung tissue and the dysfunction of pulmonary blood vessels. The airflow limitation is progressive. The clinical course of COPD is characterized by chronic disability with intermittent acute exacerbations that occur more often during the winter months. The World Health Organization has projected that COPD will rank fifth in 2020 as a global burden of disease.⁶

B. Bronchodilator drugs are central to the management of COPD

The principal action of beta agonist drugs is to relax the smooth muscle of the airways by stimulating the beta2-adrenergic receptors, which increases the cyclic AMP and produces functional antagonism to bronchoconstriction. These drugs have a very rapid onset and relatively long half-life, ranging from 4 to 12 hours depending on the formulation. There is an abundance of scientific evidence supporting combination bronchodilator therapy in COPD. The most common and effective combination therapy is a beta agonist used in conjunction with an anticholinergic (i.e., albuterol and ipratropium bromide)^{7,8}

An effective care plan for the treatment of COPD included effective management of stable COPD and the ability to manage exacerbations. Goals for effective disease management include but are not limited to: relieve symptoms, prevent disease progression, prevent and treat complications and prevent and treat exacerbations. Central to achieving these COPD management goals are appropriate and efficacious inhaled drug therapies. As stated in the *Global Initiative for Chronic Lung Disease (GOLD)* standards, bronchodilator medications are central to symptom management in COPD.⁹ Additionally the GOLD standards state:

- Inhaled bronchodilator therapy is preferred.
- The choice between beta-agonist, anticholinergic, theophylline or combination therapy depends on the individual response in terms of symptom relief and side effects.
- Combining bronchodilators may improve efficacy and decrease the risk of side effects compared to simply increasing the dose of a single bronchodilator.

Growing scientific data suggest the introduction of newer, long-acting beta-agonist bronchodilator drugs used in conjunction with inhaled glucocorticosteroids and short-acting beta-agonist bronchodilator drugs provides for highly effective control and symptom management of patients with stable COPD.

Medicare payments for inhalation drugs, particularly the beta adrenergic agonists (beta agonists), have grown steadily over the last decade. This growth in utilization and spending is not surprising given the demographics and epidemiology of this disease. While inhalation drugs do not specifically cure COPD, they can effectively manage its core symptoms in the outpatient/home setting and substantially reduce the need for more expensive and comprehensive medical interventions requiring ER visits and acute hospital admissions.

C. Comments Regarding Specific Formulation of Bronchodilator Drugs

Standard, racemic albuterol is a stereoisomer composed of a 50:50 ratio of (R) and (S) isomers. The (R) isomer is the therapeutically active bronchodilator. The (S) isomer has no bronchodilatory effect and is now believed to be paradoxical, actually opposing bronchodilation. A single isomer (R-isomer) version of albuterol, known as levalbuterol, has been FDA-approved and has been commercially available for a number of years. Levalbuterol is a safe and effective beta agonist, yet there remains only limited published evidence demonstrating levalbuterol to be more effective than racemic albuterol in COPD.

In a retrospective review, Truitt, Witko and Halpern¹⁰ compared the efficacy and outcomes in patients hospitalized with chronic obstructive pulmonary disease (COPD) or asthma. In this study, 125 patients were treated with nebulized racemic albuterol and 109 patients were treated with levalbuterol and concluded that "compared with patients treated with racemic albuterol, those treated with levalbuterol required less medication, had shorter lengths of hospital stay, had decreased costs for nebulizer therapy and hospitalization, and appear to have a more prolonged therapeutic benefit.

Nelson, Bensch, Pleskow, et al.¹¹ compared levalbuterol vs racemic albuterol and the effects on bronchodilation in a randomized, double-blinded group of 362 patients with asthma. They noted significant improvement in FEV1 with levalbuterol and concluded "levalbuterol appears to provide a better therapeutic index than the standard dose of racemic albuterol. These results support the concept that the (S)-albuterol may have detrimental effects on pulmonary function."

Schreck and Babin appearing in the American Journal of Emergency Medicine in 2005,¹² compared emergency department (ED) admission rates of patients presenting with acute asthma who were treated with either racemic albuterol or levalbuterol. The article concluded "Levalbuterol treatment in the emergency department for patients with acute asthma resulted in higher patient discharge rates and may be a cost-effective alternative to racemic albuterol." We believe this work demonstrates improved clinical efficacy when using levalbuterol.

Quinn¹³ also concludes that "Levalbuterol is a formulation containing only the R-isomer of albuterol, and clinical trials have demonstrated that it offers therapeutic advantages over racemic albuterol.

Handley et al in 2000¹⁴, a study of dose-evaluation of levalbuterol versus racemic albuterol in patients with asthma. The study results found levalbuterol to provide significant bronchodilator activity and was well tolerated. These data suggest that 0.63 mg levalbuterol provides bronchodilation equivalent to 2.50 mg racemic albuterol with less beta-mediated side effects.¹⁵

While it may be argued there is only modest evidence demonstrating the benefits of levalbuterol over racemic albuterol in COPD, it is important to note that the absence of voluminous published clinical studies does not by itself establish a lack of clinical efficacy or medical need. This kind of extrapolation on limited data is purely speculative and conflicts with current standards of clinical practice, which defer to the patient's physician the selection and prescription of the most clinically appropriate drug therapies.

AAHomecare's review of the scientific literature indicates that the use of beta agonists, including levalbuterol, for the treatment of lung disease is reasonable and necessary and should be covered by the Medicare program.

III. CONCLUSION

The scientific evidence, national and world-wide expert panel recommendations, and the current standards of care all recognize the vital role inhaled bronchodilators play in the safe, effective, and economically sound management of persons with COPD. Bronchodilators, specifically beta adrenergic agonists, are central to symptom management of COPD and must be recognized in any NCD. AAHomecare strongly recommends that CMS develop an NCD that ensures the necessary coverage of bronchodilator drugs for Medicare beneficiaries with acute and chronic lung disease.

We sincerely appreciate the opportunity to submit these comments and remain available to discuss them further with you at your convenience. Please do not hesitate to call me if you have any questions.

Sincerely,



Tyler Wilson
President & CEO

¹ The terms "inhalation drugs" in these comments are used interchangeably with "respiratory drugs." Both terms refer to drugs administered *via* a nebulizer.

² Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of COPD. National Heart, Lung, and Blood Institute. Executive Summary 2006

³ Data derived from Moran & Associates estimates from the 2001 MEPS full year consolidated file.

⁴ Centers for Disease Control and Prevention - MMWR Surveillance Summaries, August 2, 2002. No. 51/no. SS-6

⁵ Global Initiative for Chronic Obstructive Lung Disease (GOLD) of the U.S. National Heart, Lung, and Blood Institute and the World Health Organization, *Am J Respir Crit Care Med* Vol 163. pp 1256- 1276, 2001.

⁶ Murray CJ, Lopez AD. Evidence-Based Health Policy- Lessons from the Global Burden of Disease Study. *Science*. 1996; 274: 740-743. As cited by Apria HealthCare in comments submitted to CMS, September 2004.

⁷ Op cit

⁸ MacIntyre NR. COPD management: the evidence base. *Respir Care* 2001;46 (11): 1294-1303

⁹ Op cit

¹⁰ Truitt T, Witko J, Halpern M. "Levalbuterol Compared to Racemic Albuterol: Efficacy and Outcomes in Patients Hospitalized with COPD and Asthma." *Chest* 2003; 123, 1:128-135,

¹¹ Nelson HS, Bensch G, Pleskow WW, et al. "Improved bronchodilatation with levalbuterol compared with racemic albuterol in patients with asthma", *J Allergy Clin Immunol*. 1998 Dec;102 (6 Pt 1):943-52.

¹² Schreck DM, Brotea C, Shan SP. "Comparison of Racemic Albuterol and Levalbuterol in the Treatment of Acute Asthma." *American Journal of Therapeutics* 2003; 10:341-347.

¹³ Quinn C. "The Cost Effectiveness of Levalbuterol Versus Racemic Albuterol." *The American Journal of Managed Care*. July 2004, Volume 10, Number 5, Supp:S153-S157.

¹⁴ Handley DA, et al. "Dose-response evaluation of levalbuterol versus racemic albuterol in patients with asthma." *J Asthma*. June 2000; 37(4):319-27.

¹⁵ Ibid.

From: Charles B Cairns

Sent: Friday, January 19, 2007 11:17 PM
To: CMS CAGInquiries
Cc: Spencer, Francina C. (CMS/OCSQ)
Subject: Comment CAG-00354N

Attachments: Comments CAG-00354N.doc

I was unable to submit my comments today (despite multiple attempts). I have enclosed my comments and contact information as an attachment to this email.

Please contact me for any questions or for more information.

Charles B. Cairns, M.D.
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NCA for Nebulized Beta Adrenergic Agonist Therapy for Lung Diseases (CAG00354N)

COPD remains a challenging disease to manage. Beta-agonists are a mainstay of treatment for COPD patients. Recent studies suggest that beta-agonists can not only improve symptoms, but also potentially change the course of the disease. In the recent TORCH trial, combination therapy of a long acting beta-agonist with inhaled steroids can reduce mortality in patients with COPD.

However, it has become clear that there is a marked heterogeneity in both the phenotype of COPD as well as in the response to therapy. In particular, there are cases of COPD characterized by inflammation, including a prominent role of neutrophils. We have described that beta-agonists can attenuate pro-inflammatory actions of neutrophils. Relevant to the issue of isomers of beta-agonist, we found that (R)-albuterol significantly attenuated activation-induced pro-inflammatory changes in human neutrophil morphology and superoxide production. Conversely, (S)-albuterol and racemic mixtures of (R)-/(S)-albuterol did not alter activation-induced changes in neutrophil morphology. In addition, (S)-albuterol and racemate attenuated fMLP, but not PMA, activated superoxide production in neutrophils. We suggest that (R)-albuterol attenuates PMN inflammatory changes and may help to modulate inflammation. In contrast, (S)-albuterol and (R/S)-albuterol appear to enhance pro-inflammatory PMN responses, including delay of neutrophil apoptosis (Kubista, *Acad Emerg Med* 2004 11: 533)

This advantage of (R)-albuterol demonstrated in *ex vivo* neutrophil studies may have direct relevance to COPD patients with neutrophil-mediated inflammation. In a study of 234 hospitalized COPD patients, those treated with levalbuterol required less medication, had shorter lengths of hospital stay, had decreased costs for nebulizer therapy and hospitalization, and appeared to have a more prolonged therapeutic benefit when compared with patients treated with racemic albuterol. These findings support using levalbuterol as first-line therapy for hospitalized adults with COPD or asthma. (*Truit T, Chest* 2003; 123:128-135)

Thus, there is a sound phenotypic and pathophysiologic rationale for the use of an enantiomer-specific form of albuterol in COPO patients. I would encourage the CMS to continue to make levalbuterol inhalation solution available to all COPO patients on Medicare. This action would

allow physicians and patients to identify the most effective treatment for these patients and assure drug access to those patients whose care has been optimized on levalbuterol.

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In regards to the use of nonracemic molecules for the treatment of various disorders, I would like to reflect that the use of levalbuterol appears to me to have specific place for those patients with asthma and COPD.

Although most patients may respond to a racemic mixture it does appear, that a isolated chiral solution would be of benefit for patients who appear to be not responding to standard of care.

It has been a unique surprising that the use of nebulizations in asthmatics and COPD does in addition to delivery of the medication has a calming affect by having the patient focus on their disease and its treatment (removing some anxiety associated with their condition).

I am board certified in pulmonary disease and in critical care medicine and take care of many patients with COPD and asthma. Levalbuterol is a key agent in my armamentarium to treat such obstructive lung diseases. There is much literature to show its improved efficacy over conventional racemic albuterol. In addition, because it is indicated to be dosed at intervals longer than that for racemic albuterol, its overall cost is less than that of racemic albuterol. I urge you continue to support and cover levalbuterol, including both nebulized and HFA formulations, for my many patients who rely on it to maintain their quality of life. Thank you very much.

I would like to respond to the proposed nca label on levalbuterol (Xopenex) solution. I have been an emergency physician for 15 years and frequently treat acute bronchospasm in asthma and COPD in the ED and the observation unit. After reviewing the published data on the differences between racemic albuterol and levalbuterol, it is obvious that the results point to a significant advantage of using the single isomer agent. We have seen in our ER similar benefits of Xopenex in our COPD pts that are seen in the studies I have read. We use Xopenex for our pts that have failed outpatient therapy on albuterol and we use it in our 23 hour obs unit. When our pts are discharged (at a much higher rate than previous) they will go home on Levalbuterol sol when a nebulizer is available. After reviewing the literature I am sure you would agree that the pts lung function and quality of life is much better using a q6-8 hour agent with better effectiveness than an agent that has already failed them in the past. I hope you reconsider your decision to limit the availability of Xopenex for my medicare patients.

Thank you for your consideration,

Peter Stoyanoff M.D.
Clinical Assistant Professor
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Hurley Medical Center



January 19, 2007

Tiffany Sanders, MD
Francina Spencer
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Baltimore, MD 21244

**Re: NCA for "Nebulized Beta Adrenergic Agonist Therapy for Lung Diseases"
(CAG-00354N)**

Dear Dr. Sanders and Ms. Spencer:

DEY, L.P. is pleased to submit the following comments on the Medicare National Coverage Analysis for "Nebulized Beta Adrenergic Agonist Therapy for Lung Diseases" ("NCA") that the Centers for Medicare and Medicaid Services ("CMS") posted to its Web site on December 20, 2006. We know that CMS has undertaken substantial efforts over the last several years to enhance the transparency of the Medicare national coverage process, and we very much appreciate this opportunity to provide initial comments on the NCA.

DEY is a specialty pharmaceutical company headquartered in Napa, CA, that focuses on developing, manufacturing, and marketing branded and generic prescription drug products for the treatment of respiratory diseases. DEY's products help health care professionals and patients address such respiratory conditions as chronic obstructive pulmonary disease ("COPD"), asthma, and "respiratory-related allergies, such as anaphylaxis.

Overview of DEY Comments

In its comments, DEY will provide clinical information to help CMS ensure that, under Medicare's coverage policies, beneficiaries with COPD have access to appropriate nebulized therapies. While this is the main objective of our comments, we also address several threshold considerations that will help shape the context for the presentation of our clinical information.

In all, the purpose of our comments is to make five points:

1. CMS should withdraw the NCA because its scope is ambiguous. The agency should then clarify the intended subject of the review and initiate a new NCA. As currently framed, the subject of the NCA could be interpreted to be as narrow as a single compound, levalbuterol, or as broad as a full class of pharmaceuticals, beta agonists. Indeed, patient groups and other stakeholders have expressed confusion about the NCA's scope and have queried DEY on this subject. Because stakeholders are unable to understand the subject matter of CMS' action, the agency will not receive meaningful comments, thus damaging the quality of the ultimate decision and impeding progress toward a more transparent Medicare national coverage process.

2. If CMS attempts to apply the NCA to all nebulized beta agonists, the agency should address this very broad product/issue area in a thoughtful way - a way that does not impede beneficiary access to needed medications. To minimize unintended consequences of so broad an NCA, CMS should –

- *Distinguish pharmacy-compounded beta agonists from FDA-approved products;*
- *Recognize the clinical differences between nebulized short-acting and long-acting beta agonists and -- under the Global Initiative for Chronic Obstructive Lung Disease ("GOLD ") Guidelines -- the different roles these medicines play in the range of therapies patients need to manage their COPD.*
- *Refrain from review of any FDA-approved product that contains a component that, standing alone, is a beta agonist, but that, combined with another component, causes synergistic pharmacological activity that produces a "combination" medicine that has improved activity versus a beta agonist alone;*
- *Apply special precautions to avoid limiting the potential for beneficiary access to nebulized long-acting beta agonists and other future products that the GOLD Guidelines recognize are needed to provide sustained relief from COPD's effects; and*
- *Take into account other CMS initiatives that address clinical outcomes of nebulized beta agonists.*

3. COPD is a widespread, serious, and progressive disease that requires step-wise and individualized therapy depending upon a patient's symptoms and his or her tolerability to available treatment options. The standard of care prescribed in the GOLD Guidelines recognizes the importance of ensuring access of patients and physicians to planned regimens that purposely vary pharmacological interventions and accompanying delivery mechanisms.

4. While DEY believes that the NCA does not apply to combination therapies, the DuoNeb@ inhalation Solution ("DuoNeb") is nevertheless a reasonable and necessary intervention for beneficiaries with COPD. Even if the NCA were applied to all beta agonists, it would not reach DuoNeb. For while DuoNeb contains albuterol, a compound that, standing alone, is a Short-acting beta agonist, the combination of albuterol with ipratropium produces a synergistic pharmacological effect that renders DuoNeb a distinctive type of medicine – one that is not a beta agonist. Furthermore, strong clinical evidence supports the product as a reasonable and necessary intervention for Medicare beneficiaries.

5. CMS should avoid framing any national coverage decision in a way that could impede development of innovative new products. For example, DEY's nebulized formoterol (FFIS) product is a long-acting beta agonist currently undergoing FDA review, and it would be premature to include it within the scope of a national coverage decision. In the interest of completeness, DEY is supplying evidence that shows that the company's FFIS provides statistically significant and clinically relevant improvements in pulmonary function in patients with COPD relative to placebo, and that patients who were treated with FFIS demonstrated a statistically significant improvement over placebo in quality of life. FDA is encouraging manufacturers to develop innovative types of products, and Medicare coverage policies should not preempt the benefits for tomorrow's patients.

Discussion

1. CMS should withdraw the NCA because its scope is ambiguous. The agency should then clarify the intended subject of the review and initiate a new NCA.

Summary Point: It would be difficult for any stakeholder relying on the CMS tracking sheet to understand the subject matter of the NCA. For that reason, the agency will not receive the kinds of robust, thoughtful comments needed to inform a Medicare national coverage decision.

It is DEY's understanding that the tracking sheet CMS posted December 20 is the only public document describing the NCA. As such, we will use this document as the basis for framing threshold issues for CMS' consideration.

Our central point is that it is difficult to understand from the tracking sheet the exact scope of the NCA. The sheet's title refers to "Nebulized Beta Adrenergic Agonist Therapy for Lung Diseases." The contents of the sheet itself, however, seem focused on COPD.

Moreover, in one passage of the tracking sheet the agency states:

"CMS has internally generated a formal request for a National Coverage Analysis to determine when treatment with a nebulized beta adrenergic agonist is reasonable and necessary for Medicare beneficiaries with COPD."

In another passage, the tracking sheet uses the following language:

"CMS initiates an NCA on the use of nebulized levalbuterol for the treatment of COPD in the Medicare population."

Though each purports to describe the scope of the NCA, the two statements in the tracking sheet stand in stark contrast to one another. On the one hand, "nebulized levalbuterol" is a particular compound. On the other hand, "beta agonist" is a class of drugs that encompasses many individual compounds, including levalbuterol. Thus, based on the tracking sheet, we believe it is difficult to determine the exact scope of issues on which CMS seeks comments. Indeed, patient groups and other stakeholders have expressed confusion about the NCA's scope and have queried DEY on this subject.

We understand from informal discussions with officials of the Coverage and Analysis Group (CAG) that the intent of CMS in initiating the NCA was to address beta agonists generally. We very much appreciate this information. However, we are concerned that the formal basis for public comments remains the Web-posted tracking sheet, which, because it is ambiguous, seems inconsistent with the kind of transparent national coverage process that CMS has sought to foster. Indeed, because it would be difficult for any stakeholder relying on the tracking sheet to understand the subject matter of the NCA, we fear that CMS will not receive the kinds of robust, thoughtful comments needed to inform the agency's actions.¹ In turn, this will limit the agency's ability to render an informed decision.

For these reasons, we recommend that CMS withdraw the NCA; reframe it so that its scope is clearly described; then open a new NCA with a new opportunity for initial public comments.²

These actions are necessary to ensure that all interested parties, including groups representing COPD sufferers, have an opportunity to be heard on this critical patient-care issue.

2. If CMS attempts to apply the NCA to all nebulized beta agonists, the agency should address this very broad product/issue area in a thoughtful way – a way that does not impede beneficiary access to needed medications.

Summary Point: *It may be unprecedented for CMS to attempt to make an entire class of pharmaceuticals the subject of a Medicare national coverage review. The agency should therefore carefully tailor its review to those areas most relevant to clinical outcomes for Medicare beneficiaries.*

Because the current tracking sheet is ambiguous, DEY believes that, for purposes of filing timely comments, it must assume the broadest construction of the NCA -- i.e., that it potentially applies to the entire class of nebulized beta agonists. We wish to emphasize our fundamental view that the tracking sheet is unclear. We assume a broad construction of the NCA only for purposes of filing these comments.

If the NCA is interpreted to apply to all nebulized beta agonists supplied within Medicare's Part B Durable Medical Equipment (DME) benefit, we believe it is important for CMS to rely on thoughtful principles to address this very broad product/issue area in a manageable way. Indeed, we are uncertain whether there is any precedent for CMS to attempt to make a full class of pharmaceuticals the subject of an NCA.

Below, we identify principles that should guide CMS in carrying out such a broadly structured NCA:

a. Distinguish Pharmacy-Compounded Beta Agonists from FDA-Approved Products

Products approved for marketing by FDA are manufactured in accord with specified FDA requirements, such as current Good Manufacturing Practices (GMPs), which are designed to ensure a drug's quality, purity, strength, and other characteristics it is represented to possess. In contrast, pharmacy-compounded beta agonists are not reviewed, evaluated, or manufactured under FDA regulatory controls. For this reason, medication errors and inaccurate dosing are more likely to occur.

In cases in which compounded drugs are being produced in violation of the Federal Food, Drug, and Cosmetic Act, it is clear that "Medicare does not pay for the drugs because they do not meet the FDA approval requirements of the Medicare program."³ However, even pharmacy-compounded drugs not unlawful under FDA requirements cannot be covered by Medicare unless they satisfy the statute's "reasonable and necessary" standard.⁴

In recent policy changes, Medicare has recognized the significance of the distinction between pharmacy-compounded and FDA-approved beta agonists. Specifically, CMS has recognized the potential for "substitution of compounded forms of inhalation drugs . . . in instances where such a substitution may not be justified by . . . issues of medical appropriateness . . ."⁵

Previously, CMS had few tools to identify pharmacy-compounded drugs among the services for which reimbursement was claimed by Part B suppliers. Now, however, Medicare has revised its Healthcare Common Procedure Coding System (HCPCS) Level II codes for nebulized drugs "to

distinguish FDA-approved, non-compounded final products from compounded inhalation solutions”⁶ - a step that “provide[s] the basis for assessing” the desirability of “articulate[ing] clinical standards for use of compounded drugs as opposed to non-compounded drugs...”⁷

In all, the coding system now provides the tools for CMS to isolate and evaluate claims for services associated with pharmacy-compounded beta agonists.⁸ As such, DEY recommends that CMS, in evaluating Medicare coverage within the potentially broad parameters of the NCA, give focused attention to the medical necessity of pharmacy-compounded beta agonists.

- b. Recognize the clinical differences between nebulized short-acting and long-acting beta agonists and -- under the Global Initiative for Chronic Obstructive Lung Disease ("GOLD") Guidelines -- the different roles these medicines play in the range of therapies patients need to manage their COPD.

There are two main types of beta agonists: short-acting beta agonists, such as albuterol, and long-acting beta agonists, such as formoterol. Both of these types of beta agonists are critical to caring for COPD patients - a fact explicitly recognized by the GOLD Guidelines, which were established by the U.S. National Heart, Lung, and Blood Institution and the World Health Organization. The GOLD guidelines represent the standard of care for COPD patient-care management.

The GOLD Guidelines suggest a stepwise, additive pharmacologic approach to therapy in order to address the chronic, progressive nature of COPD. As we explain in more detail later in our comments, patients who have not advanced beyond Stage I (Mild) COPD might be able to control their symptoms with a short-acting beta agonist alone. However, as a patient's COPD progresses, long-acting beta agonists or combination therapy may need to be included in their treatment regime, while also relying on a short-acting beta agonist to control exacerbations.

In attempting to address an NCA that spans the full nebulized beta agonist class, CMS should keep in mind the importance of ensuring that patients have access to the range of therapies needed to manage their COPD effectively. The GOLD guidelines recognize this fact, and so should Medicare's coverage policies.

- c. Retrain from review of any FDA-approved product that contains a component that, standing alone, is a beta agonist, but that, combined with another component, causes synergistic pharmacological activity that produces a "combination" medicine that has improved activity versus a beta agonist alone.

"Combination" drug products are FDA-approved, fixed-dose medicines comprised of two pharmaceuticals manufactured in compliance with GMP requirements. FDA is encouraging manufacturers to develop these innovative types of products. For purposes of Medicare, even if the NCA were construed to apply to all nebulized beta agonists, it would not encompass combination products.

To understand the reason for this, it is important to recognize that combination products do not simply offer a convenient means for dispensing two separate drugs. Instead, they rely on the combined effects of the two pharmaceuticals to produce a *synergistic pharmacological activity* that neither drug could produce alone. Thus, the combination product is clinically and fundamentally different than either of its component parts.

Considered in this light, a pharmaceutical that, standing alone, is a beta agonist, cannot be combined with another pharmaceutical - even another beta agonist - to render the resulting combination product a beta agonist. As we explain in more detail below, the GOLD Guidelines recognize the importance of providing patients combinations of medicines to optimize clinical results. DuoNeb, for example, though containing albuterol, is not a beta agonist. This is because the combination of albuterol with the product's other component - ipratropium - produces a pharmacological result altogether distinct from that produced by a beta agonist.

It would therefore be overly broad - and clinically inaccurate - to attempt to subject nebulized combination products to the NCA. We explain this topic in more detail, below, as we address DuoNeb.

d. Apply special precautions to avoid limiting the potential for beneficiary access to nebulized long-acting beta agonists and other future products that the GOLD Guidelines recognize are needed to provide sustained relief from COPD's effects.

Any NCA that seeks to address so broad a clinical field as nebulized beta agonists holds strong potential for producing unintended consequences. We therefore suggest that CMS carefully consider ways to limit its clinical conclusions to areas where, indeed, the facts are discernible. Our specific concern pertains to innovation and future nebulized beta agonist products.

DEY is aware that Medicare's coverage policies typically correspond to categories of items and services. As such, coverage policies, by their nature, typically encompass multiple individual products. However, the current NCA, by purporting to address an entire *class* of pharmaceuticals, raises the specter of an ultimate national coverage decision so broad as to sweep in products for which it is not yet realistic to evaluate medical necessity. In such an instance, the result would be to land a blow against high quality care from which future patients could not easily recover. In the longer term, the result could be to dampen the incentive of companies like DEY to innovate.

For example, trends in drug development suggest the growing importance of long-acting beta agonists that offer patients sustained relief from COPD's effects. Similarly, the GOLD Guidelines recognize the key role these long-acting beta agonists can play in an effective care regimen. As explained in more detail later in these comments, one DEY research initiative concerns nebulized formoterol fumarate - a long-acting beta agonist. DEY has sponsored a number of clinical studies on this product, and it is now under review by FDA.

Currently, there is no FDA-approved nebulized formoterol product in commercial use. There is, however, nebulized formoterol that is pharmacy-compounded.⁹ Consistent with our comments, above, on pharmacy-compounded beta agonists, CMS could conclude that Medicare coverage for pharmacy-compounded formoterol should be withdrawn or limited. DEY is concerned that some might erroneously interpret this type of decision to extend to future FDA-approved formoterol products.

Therefore, to minimize unintended consequences, we urge CMS to frame its ultimate "reasonable and necessary" conclusions in language that is as precise as possible. We further urge CMS to articulate its policies in a way that cannot be interpreted as encompassing long-acting nebulized beta agonists and other nebulized products not ripe for coverage review.

d. Take into account other CMS initiatives that address clinical outcomes associated with nebulized beta agonists.

It is also important in managing an NCA in so potentially expansive a clinical field as nebulized beta agonists to take into account other CMS initiatives that may offer useful information and lessons. Such an approach can also help CMS manage its resources by avoiding activities that are duplicative and inappropriately preemptive.

For example, CMS has recently announced a demonstration project to "test the impact of care management services provided to beneficiaries who require inhalation therapy drugs administered via nebulizer under Part B of the Medicare program."¹⁰ Among the objectives of the demonstration is to determine whether better coordination of services "leads to improvements in health status ..."¹¹

DEY strongly supports this demonstration. Indeed, we have undertaken our own policy and clinical examination of whether Medicare services associated with inhalation drugs might be organized in a way more conducive to improved beneficiary outcomes.

We recognize, of course, that while the current Part B demonstration addresses a relatively broad set of issues, the national coverage process is focused on whether individual items and services are reasonable and necessary within the meaning of the Medicare statute. At the same time, however, CMS has long articulated the view that reasonable/necessary determinations often hinge on the conditions under which care is provided, such as the qualifications of the health professionals and facilities that provide it.¹²

We therefore suggest that CAG carefully consider the current inhalation drug demonstration and seek to identify clinical issues where the demonstration's objectives and those of the NCA intersect. To the extent such intersections are identified, we recommend that CAG proceed cautiously, avoiding actions under the NCA that could duplicate - or, as a practical matter, preempt -- those in the demonstration.

To the extent there is risk of duplication or preemption, we suggest that CAG defer action under the current NCA to allow the broader review under the demonstration to proceed. Then, once the findings of the demonstration are available, CAG could initiate a more targeted NCA that addresses any needs that the demonstration identifies.

3. COPD is a widespread, serious, and progressive disease that requires step-wise and individualized therapy depending upon a patient's symptoms and his or her tolerability to available treatment options.

Summary Point: COPD is a prevalent, debilitating disease within the Medicare population. Current treatment guidelines recommend an individualized and progressive approach when treating COPD. In order to meet this standard of care, patients and physicians must have access to current and future COPD medications that treat COPD with deliberately varying pharmacological and drug delivery mechanisms.

A. Background on COPD and COPD patients.

i. COPD is a severe, debilitating, and progressive disease.

COPD is a major health problem in the U.S. In recognition of this, the U.S. National Heart, Lung, and Blood Institute and the World Health Organization established the Global Initiative for Chronic Obstructive Lung Disease ("GOLD") in 1998, and charged GOLD with increasing awareness of COPD and helping the millions of patients who suffer from this disease and die prematurely from its complications.¹³ In December 2006, GOLD published its *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*, which summarizes the current state of the COPD field, including issues such as defining the disease, epidemiology, and treatment.

According to the GOLD Guidelines, COPD is characterized by chronic airflow limitation, pathological changes in the lung, certain significant extra-pulmonary effects, and comorbidities that may contribute to the severity of the disease.¹⁴ While COPD is preventable and treatable, its pulmonary component is characterized by airflow limitation that is not fully reversible. An airflow limitation of this type is usually progressive, particularly if a patient is exposed to noxious particles or gases. A patient's COPD is classified in one of four stages of severity: Mild (I), Moderate (II), Severe (III), and Very Severe (IV). In its late stages, COPD may be life-threatening, and a patient's quality of life is appreciably impaired.

ii. *COPD, and in particular more severe stages of the disease, is widespread in the Medicare population.*

The GOLD Guidelines also highlight the prevalence of COPD. COPD is currently the fourth leading cause of death in the United States, and experts expect increases in its prevalence and mortality in the coming decades. An estimated 11-12 percent of the U.S. population suffers from COPD,¹⁵ affecting roughly 30 million Americans¹⁶ (only half of whom are diagnosed).¹⁷ The seriousness of COPD is underscored by the fact that in 2000 the disease precipitated some 1.5 million emergency department visits¹⁸ and some 726,000 hospitalizations.

Of the currently diagnosed COPD population, slightly over half (53 percent) are part of the Medicare population.²⁰ And of these, 9.3 percent are diagnosed with mild COPD, 36.6 percent with moderate COPD, 30.4 percent with severe COPD, and finally 23.7 percent with very severe COPD.²¹ Thus the majority of Medicare beneficiaries with COPD suffer from severe or very severe stages of the disease. COPD is also a debilitating illness within the Medicare population. In Medicare, COPD patients are not only elderly, but quite often frail, even fragile. As patients have told us: "When you can't get enough air, you are helpless."

COPD is complicated by the fact that patients frequently fail to comply with their therapeutic regimens, and this lack of compliance is associated with poor prognoses.²² The compliance challenges COPD patients face are highlighted by the fact that they are often prescribed as many as five to eight oral and inhaled medications to be taken at different intervals,

either regularly or as needed.²³ Moreover, the more serious the stage of COPD, the more medications a patient will take,²⁴ thus resulting in the most frail patients having to juggle the most complicated and time-consuming treatment regimens.

B. Background on COPD treatment.

i. Current and future treatments for COPD include short- and long-acting beta agonists and combination therapy.

Inhaled bronchodilators are the foundation for COPD management. These medications alleviate symptoms, reduce the frequency of disease exacerbations, and improve a patient's quality of life.²⁵ There are two key classes of inhaled bronchodilators: beta agonists, such as albuterol, and anticholinergics, such as ipratropium.

There are also two main types of beta agonists: short-acting beta agonists, such as albuterol, and long-acting beta agonists, such as formoterol. Both of these types of beta agonists are critical to caring for COPD patients. Due to the chronic, **progressive** nature of the disease, the GOLD Guidelines suggest a stepwise, additive pharmacologic approach to therapy.²⁶ For example, patients who have not advanced past Stage I (Mild) COPD might be able to use only a short-acting beta agonist to control their COPD symptoms.²⁷ As a patient's COPD progresses, the patient may add long-acting beta agonists or combination therapy to their treatment regime, while also relying on a short-acting beta agonist to control exacerbations.²⁸ It's critical that patients have access to the range of therapies in order to manage their COPD effectively.

As explained below, COPD patients may also be treated via different delivery mechanisms, with may also depend on effectiveness and a patient's ability to use and preference for a particular mechanism.

ii. Nebulized therapy is critical to caring for Medicare beneficiaries with COPD.

a. Many patients do not use inhalers correctly, and for these patients, access to nebulized therapy is critical.

Access to nebulized COPD medication is critical to many COPD patients, particular those with later, more severe stages of COPD. For these patients, ease of administration is an important consideration in selecting the right COPD medication. As the GOLD Guidelines note, "COPD patients may have more problems in effective coordination and find it harder to use a simple metered-dose inhaler (MDI) than do healthy volunteers or asthmatics", which highlights the need for simple, effective delivery options such as nebulization.²⁹

Studies have suggested that up to 70 percent of patients fail to use MDIs properly.³⁰ In observational studies of MDIs and dry-powder inhalers

used in clinical practice, it has been reported that the majority of patients used their inhalers ineffectively (88.9 percent of patients made at least one mistake in the **inhalation** technique).³¹ Of these, over 22 percent performed errors that were critical for reliable drug delivery to the lungs. The use of DPIs was associated with a similar percentage of inadequate inhalation techniques as the use of MDIs in clinical practice.³² These studies also confirmed the findings of a previous study,³³ which demonstrated that inadequate inhalation techniques were employed by older patients.

The clinical literature also shows that many elderly patients are simply unable to learn how to use an MDI.³⁴ For example, a study of inhalation profiles in asthmatics and COPD patients revealed the majority of patients used a MDI incorrectly, and 40 percent exhibited inadequate hand-lung coordination.³⁵ The study further identified a group of patients with severe COPD in which 7 to 19 percent of the patients were not able to generate optimum flows for drug delivery through simple DPIs.³⁶ The investigators of the study recommended a flow-independent delivery system, such as nebulization, for this population.³⁷

Difficulty with coordination can be compounded when a caregiver is involved, as is sometimes the case with Medicare beneficiaries and those suffering from severe stages of COPD. Specifically, when COPD patients are dependent on caregivers' training and ability, coordination of actuation and inhalation and appropriate dosing becomes more difficult.³⁸

Moreover, cognitive impairment is one of the most common nonrespiratory effects of COPD,³⁹ and such impairment can exacerbate a patient's inability to comply fully with their prescribed treatments. In turn, failure to comply with a therapeutic regimen can worsen the patient's COPD, which may negatively affect cognitive impairment - it's a vicious cycle. For patients with cognitive impairments, nebulized medications may be their only viable treatment option.

b. Many patients prefer nebulizers.

Studies have also demonstrated patient preference for nebulized COPD therapy. In a long-term prospective study of home nebulizer treatment, 65 percent of patients expressed a preference for nebulized therapy over therapy with an MDI alone or an MDI with a Nebuhaler spacer.⁴⁰ Similarly, in a survey of patients' views of home nebulizer treatment for chronic lung disease, patients overwhelmingly (98.2 percent) agreed that the benefits of using a nebulizer far outweighed the potential disadvantages, and nearly three quarters (70.7 percent) found the nebulizers superior to their inhalers in symptom relief.⁴¹ Importantly, for patients who used *both* an inhaler and a nebulizer, 76 percent indicated that the nebulizer was better than the inhaler, attributing this to a variety of factors, such as efficacy, dosing, usage, onset of action, and ease of use.

Anecdotal evidence also suggests that nebulized treatment is an indispensable part of COPD therapy. For example, patients have told us that they have found that nebulizers are easier to use and handle and that they felt relief more quickly from the nebulized treatments, with longer lasting effects, than from the inhalers.

As a standard of care, nebulization continues to be used easily and effectively and is an important treatment option for clinicians and patients.

iii. DEY's current and future COPD products provide patients with important treatment options.

Because beta agonists and anticholinergics are important aspects of treatment, DEY has developed a commercial product that improves clinical outcomes by administering albuterol and ipratropium in combination. This product - the patented and FDA-approved DuoNeb Inhalation Solution ("DuoNeb") -- delivers the albuterol-ipratropium combination of medications to patients by nebulizer. Additionally, DEY is actively developing other types of combination therapies to treat COPD. Indeed, the GOLD Guidelines and FDA recognize and encourage such innovation. New formulations and delivery methods for COPD treatments will improve patient treatment and compliance.

DEY is also currently seeking FDA approval of Formoterol fumarate ("Formoterol"), which is a long-acting, selective beta agonist used in the treatment of patients with asthma and COPD. Relative to other beta adrenergic bronchodilators, Formoterol is unique in that it has a rapid onset of action similar to short-acting bronchodilators (within five minutes),⁴² and prolonged duration of action (greater than 12 hours).⁴³ Currently, the only FDA-approved presentation of Formoterol is a dry powder capsule formulation for oral inhalation with the Aerolizer[®] dry powder inhaler (DPI). DEY has developed a Formoterol Fumarate Inhalation Solution ("FFIS") delivered via nebulization for maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema. Alternatives to DPI for the administration of Formoterol, such as nebulization, will allow treatment of patients who are unable to generate sufficient airflow for efficient drug delivery from a DPI. Once approved, DEY's FFIS product will provide an important treatment option for COPD patients.

C. Treating COPD requires an individualized approach, based on a patient's response to, ability to use, and preference for a particular therapy.

Treating COPD is not a "one size fits all" approach. The GOLD Guidelines recognize that in order to address COPD symptoms and manage quality of life effectively, COPD patients must receive an individualized approach to managing their COPD.⁴⁴ While several classes of medications exist for treating COPD, the choice within each class should depend upon the availability of medication and the patient's response to it.⁴⁵ Moreover, as discussed above, because of its progressive nature, COPD should be treated

in a step-wise fashion, with medications added as needed in proportion to the severity of the disease and the patient's symptoms.

Patient preference and ability to use the medicine's delivery mechanism is also important. A variety of studies comparing nebulized delivery to MDIs and dry powder inhalers have demonstrated similar efficacy as to nebulizers and have therefore recommended that delivery-device selection be based on patient factors, such as the ability to use the device correctly and patient preference.⁴⁶ As recommended by the GOLD Guidelines: "The choice between a [beta] agonist, anticholinergic, theophylline, or combination therapy depends on availability and individual response in terms of symptom relief and side effects."⁴⁷

Medicare beneficiaries should therefore have access to all available medications, in order to enable their physicians to tailor their individual treatments and thus provide optimum care. In addition, we believe that inherent in the cost-effectiveness of the therapy is the patient's ability to comply with prescribed treatment regimens.

Additionally, through better patient compliance, costs are reduced because of the reduced number of hospitalizations and emergency room visits, as well as through a reduced volume of physician visits associated with pharmacy switching.

D. The application of the NCA to combination products and beta agonists generally is ambiguous.

As noted above, albuterol, a beta agonist, is one component of DuoNeb. Innovation is also rapidly occurring with respect to other combination therapy products that may contain a beta agonist as one component. DEY does not believe the stated scope of the NCA clearly extends to a product that nebulizes a combination of drugs, of which only one is a beta agonist. DEY also strongly believes that such application could harm future innovation and thus patient care.

The NCA is also ambiguous regarding its applicability to nebulized beta agonists generally. That said, we will, consistent with the threshold considerations identified above, assume the broadest conceivable construction of the NCA for purposes of filing these comments. Accordingly, in the materials below, we provide clinical information on DuoNeb and Fonoterol and address the medical necessity of those products.

E. Combination therapies of which one component is a beta agonist are not, scientifically speaking, beta agonists.

The pharmacological action and clinical benefit for combination therapies for the treatment of COPD are distinctly different than for a beta agonist alone. As compared to beta agonists, combination therapies for the treatment of COPD are different products for a different class of patients. Combination therapies rely on the combined effects of more than one pharmaceutical to produce a *synergistic pharmacological activity* that its components could not alone produce. Thus, the combination product is clinically and fundamentally different than its component parts.

Because of these differences, there has been confusion among stakeholders with regard to whether the NCA includes combination therapies within its scope. These stakeholders may have assumed that the NCA did not apply to these combination therapies and

therefore unknowingly did not comment on the NCA. This simply is not fair to stakeholders, including Medicare beneficiaries. It also prevents the coverage process from having the transparency that it requires.

4. While DEY believes that the NCA does not apply to combination therapies, DuoNeb is nevertheless a reasonable and necessary intervention for beneficiaries with COPD.

Summary Point: *Albuterol, a short-acting beta agonist when standing alone, is only one component of DEY's DuoNeb, and is combined with other active ingredients in nebulized form to achieve a synergistic effect. For this reason, DEY believes that the NCA does not and should not apply to DuoNeb. However, for the sake of completeness, we are summarizing the relevant clinical evidence - a review of which demonstrates that DuoNeb is reasonable and necessary for the treatment of COPD.*

A. Overview of DuoNeb

DuoNeb is a sterile, non-allergenic, premixed combination drug (ipratropium bromide and albuterol sulfate) that enhances patient safety by minimizing the risk of medication errors. DuoNeb eliminates the need for Medicare beneficiaries to nebulize two different bronchodilators, resulting in better overall clinical efficacy, reduced patient confusion, improved patient compliance, lower error rates, and faster treatment times.

DuoNeb enhances compliance and safety by providing patients with albuterol and ipratropium in a single, ready-to-use vial for nebulization. As discussed in more detail below, DuoNeb was shown to achieve a 24 percent improvement in peak FEV₁ compared with albuterol alone ($p < 0.001$), and 37 percent improvement over the ipratropium group ($p < 0.0001$).⁴⁸ Moreover, by eliminating the need for Medicare beneficiaries to nebulize two different bronchodilators, DuoNeb results in better overall clinical efficacy, reduced patient confusion, improved patient compliance, lower error rates, and faster treatment times.

Importantly, while DuoNeb helps a range of COPD patients, nearly 60 percent of the product's uses are associated with patients who have severe forms of the illness.⁴⁹ For the sickest of Medicare's COPD population, DuoNeb is often the therapy offering the most benefit. For these severely ill patients, access to DuoNeb is literally a lifeline - the one therapy that allows their lives to move forward, despite the debilitating disease from which they suffer.

B. Overview of FDA and Medicare/other coverage status.

DuoNeb was approved by FDA in March 2001, and it has been covered and reimbursed under Medicare's Part B DME benefit since the product was first commercialized. DuoNeb is the only fixed-dose, combination therapy product that FDA has approved for COPD. Thus, when Medicare covers DuoNeb for COPD, it is covering an FDA-approved, "on-label" use.

DuoNeb is also covered in 33 state Medicaid programs, as well as by over 4,000 private insurance plans in every region of the country. Importantly, many of these

private plans admitted DuoNeb to their formularies only after determining that the product was medically necessary.

C. The clinical literature affirmatively supports the medical necessity of DuoNeb.

DuoNeb enhances compliance and safety by providing patients with albuterol and ipratropium in a single, ready-to-use vial for nebulization. By eliminating the need for Medicare beneficiaries to nebulize two different bronchodilators, DuoNeb results in better overall clinical efficacy, reduced patient confusion, improved patient compliance, lower error rates, and faster treatment times. Importantly, while DuoNeb helps a range of COPD patients, nearly 60 percent of the product's uses are associated with patients who have severe forms of the illness.⁵⁰ For the sickest of Medicare's COPD population, DuoNeb is often the therapy offering the most benefit. For these severely ill patients, access to DuoNeb is literally a lifeline - the one therapy that allows their lives to move forward, despite the debilitating disease from which they suffer.

Albuterol and ipratropium each offer important clinical benefits. Albuterol, a beta agonist, provides peripheral airway bronchodilation⁵¹ and stimulates mucociliary function.⁵² Ipratropium, an anticholinergic, provides central airway bronchodilation⁵³ can help a patient sleep better,⁵⁴ and, as an element of extended therapy, can improve baseline lung function.⁵⁵ While albuterol and ipratropium each offer benefits standing alone, clinical data demonstrate that using them in combination - that is, nebulizing them together, in planned proportions, at the same time - yields clinical results superior to those produced by either agent alone.⁵⁶

*i. **Gross, et al.***

Pursuant to FDA's regulations, FDA's approval of DuoNeb recognizes that the product combines albuterol and ipratropium in a way that allows each agent to contribute to the intended therapeutic effect,⁵⁷ even to provide additive efficacy, but without providing effects that are duplicative. Integral to FDA's pre-market approval of DuoNeb was a finding that the product's efficacy represented a significant and statistically verifiable improvement over the efficacy of using ipratropium and albuterol individually. This improvement was demonstrated in a prospective, double-blind, crossover multicenter trial involving 863 patients over a 12-week period. The results achieved by DuoNeb were significantly superior and unmistakable:

- 24 percent improvement in peak FEV₁ compared with albuterol alone (p <0.001);
- 37 percent improvement over the ipratropium group (p <0.001).⁵⁸

*ii. **Levin, et al.***

Additionally, in a randomized, double-blind, placebo-controlled study of 195 patients, investigators reached the conclusion that

the combination of ipratropium with albuterol "resulted in a combination regimen that was safe and provided a more effective bronchodilation profile than albuterol alone." ⁵⁹ Ultimately, the study documented "the usefulness of adding ipratropium bromide inhalant solution to albuterol for patients with COPD requiring small volume nebulizer treatments", concluding that "[t]his combination should be considered first-line therapy." In sum, this study shows that by activating multiple mechanisms of action, combination therapy provides greater bronchodilation, ⁶⁰ and other studies have shown that it does so without increasing toxicity or adverse reactions.⁶¹

iii. **The GOLD Guidelines.**

The GOLD Guidelines also recognize that "[c]ombining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilation for equivalent or lesser side effects." ⁶² In support of this statement, the Guidelines give the example of a short-acting beta agonist and an anticholinergic, which provides greater and more sustained improvements in FEV₁ than either drug alone, and which does not product evidence of tachyphylaxis over ninety days of treatment.⁶³ The Guidelines also recognize that the combination of a beta agonist with an anticholinergic (with or without theophylline) "may produce additional improvements in lung function and health status." ⁶⁴

The GOLD Guidelines suggest a stepwise, additive pharmacologic approach to therapy for COPD due to its chronic, progressive nature, and FDA is encouraging manufacturers to develop these innovative types of products. Consistent with this, industry is researching and developing treatments, particularly combination products, that may be used to treat COPD. These future treatments may enable better treatment of COPD than ever before due to the ability of combination therapy to achieve a synergistic effect between the combined medications. Medicare beneficiaries should have access to the range of treatments for COPD as needed for therapeutic compliance, ease of administration, and individual effectiveness.

D. DuoNeb enhances patient compliance by reducing the overall number of medications COPD patients must take.

As described above, COPD patients are often prescribed as many as five to eight oral and inhaled medications to be taken at different intervals, either regularly or as needed.⁶⁶ Data show that an inverse relationship exists between patient adherence to therapy and the complexity of a drug regimen.⁶⁷ Unfortunately - but not surprisingly - COPD patients often fail to comply with this complex therapeutic regimen, and this lack of compliance is associated with poor prognoses.⁶⁸ Moreover, the patients with the most severe and debilitating COPD are also the patients who must cope with the most complicated treatment regimens. These data suggest the importance of

simplifying treatment regimens as much as possible.⁶⁹ For many patients, DuoNeb helps ease this burden, thus increasing compliance with their therapeutic regimen and bettering their overall health.

DuoNeb is within the class of therapies known as "fixed-dose combination" (FDC) treatments. In addition to their clinical- and compliance-related benefits, FDCs - because they are FDA-approved products manufactured under GMPs -- reduce the risks associated with separate administration of their component medications. Therapy simplification is among the key strategies for enhancing patients' compliance with their therapeutic regimens. The simpler the regimen, the greater the degree of compliance.⁷⁰ Moreover, the risk of medical errors and other adverse events declines as the number of medication doses is reduced. Indeed, as mentioned above, FDA is encouraging manufacturers to develop these innovative types of products.⁷¹ Among other advantages, these fixed-dose combinations can replace pharmacy compounding of individual drugs. As noted above, pharmacy-compounded drugs do not offer the patient safety protections of FDA regulation.⁷²

As an FDC product, DuoNeb avoids the need for a COPD patient to manually handle separate vials of albuterol and ipratropium. With DuoNeb, there is no need to handle individual vials of albuterol and ipratropium and then to manually measure and/or mix the two drugs. Instead, the two medications have been combined into a single drug product, manufactured in accord with FDA requirements and, upon a physician's prescription, are ready for nebulization by patients.

In the event of a non-coverage decision for DuoNeb, physicians would prescribe - and COPD patients would use - separate, individual vials of albuterol and ipratropium rather than the FDA-approved, clinically superior combination drug product, DuoNeb. Non-coverage of this combination therapy would make compliance even more difficult by inducing beneficiaries to integrate separate dose vials of albuterol and ipratropium into their treatment regimens. Doing this would not only take beneficiaries more time,⁷³ but would also put their compliance and prognoses at significant additional risk. This risk would be even more serious for hospital inpatients who use DuoNeb and who, upon discharge and entry into Medicare Part B, would face a drastically new regimen.

B. Background on Formoterol.

Formoterol fumarate ("Formoterol") is a long-acting, selective beta agonist used in the treatment of patients with asthma and COPD. Relative to other beta adrenergic bronchodilators, Formoterol is unique in that it has a rapid onset of action similar to short-acting bronchodilators {within five minutes},⁸⁰ and prolonged duration of action (greater than 12 hours).⁸¹ The recently-issued GOLD Guidelines recommend the administration of a long-acting beta agonist, such as formoterol fumarate, to control symptoms in patients with Stage II to Stage IV COPD, as this treatment is considered more effective and convenient than treatment with short-acting bronchodilators.⁸²

In the United States, the only FDA-approved presentation of Formoterol is a dry powder capsule formulation for oral inhalation with the Aerolizer® dry powder inhaler (DPI). Alternatives to DPI for the administration of Formoterol, such as

nebulization, will allow treatment of patients who are unable to generate sufficient airflow for efficient drug delivery .

DEY has researched and developed a Formoterol Fumarate Inhalation Solution ("FFIS") delivered via nebulization for maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema. DEY's studies have demonstrated that FFIS is well tolerated and will provide a safe and effective option for COPD patients requiring long-acting maintenance bronchodilator therapy. DEY's FFIS treatment also showed a statistically significant improvement over placebo in quality of life. DEY has filed a New Drug Application with FDA for its FHS product, which is currently undergoing FDA review. Once approved, DEY's FFIS product will provide an important treatment option for COPD patients.

C. Clinical data support the medical necessity of nebulized formoterol for the treatment of COPD.

DEY has conducted three randomized, double-blind studies to support the efficacy and safety claim for use of Formoterol Fumarate Inhalation Solution ("FFIS") delivered via nebulization for maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema. DEY's studies have consisted of two dose-ranging studies and a pivotal safety and efficacy trial. DEY also conducted a one-year open-label study in an additional 569 patients, which confirmed the long-term safety of FFIS and provided comparative data to Foradil®. Results from the pivotal trial demonstrated that administration of FFIS by nebulization was well tolerated and will provide a safe and effective option for COPD patients requiring long-acting maintenance bronchodilator therapy. Additionally, patients in the pivotal study who were treated with DEY's FFIS demonstrated a statistically significant improvement over placebo in quality of life.

*i. **Administration of FFIS will provide a safe and effective option (or COPD patients requiring long-acting maintenance bronchodilator therapy.***

The pivotal study used a multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled, parallel-group design. The primary objective of the study was to demonstrate the efficacy and safety of FFIS 20 mcg when compared to placebo. A total of 437 COPD patients were enrolled. Of these, 209 patients received at least 1 dose of FHS. Participants were adult patients (male and female) with COPD (mean age 62.8 to 67.1 years, overall range 40 to 86 years), who had a current or prior smoking history of at least 10 pack-years. Patients with a forced expiratory volume at 1 second (FEV₁) less than 70 percent but at least 30 percent of predicted normal and a FEV₁/ forced vital capacity (PVC) ratio of less than 70 percent prior to randomization were eligible to enter.

Patients were treated in 1:1:1 ratio with FFIS 20 mcg administered by the Pari-LC-Plus~ nebulizer and PRONEB compressor system, Foradil Aerolizer~ (FA) 12 mcg, or placebo twice daily for 12 weeks. The active treatment, FA, was primarily included in the design as validation of efficacy in relation to placebo. A twice-daily dosing regimen was

selected based on previous experience with the active drug, reference literature, and the FDA-approved dosing regimen for FA.

The study demonstrated that DEY's FFIS 20 mcg provides statistically significant and clinically relevant improvements in pulmonary function in patients with COPD relative to placebo. No statistically significant differences were observed between FFIS 20 mcg and the currently-approved treatment, which indicates that the two active formulations of Formoterol provide similar improvement in pulmonary function in the target population.

ii. ***Patients treated with FFIS showed a statistically significant improvement in quality of life.***

Patients treated with DEY's FFIS 20 mcg demonstrated statistically significant improvement over placebo in quality of life versus patients who received the currently-approved treatment.⁸³ The degree of quality of life improvement was considered clinically significant (change ≥ 4 pts) with DEY's FFIS 20 mcg, but not with the currently marketed treatment. These results indicate a potential advantage of DEY's FFIS formulation over what is currently on the market.

The advantage may be due to additional benefits derived from nebulized drug delivery, because, as discussed above, nebulization is associated with greater perceived efficacy, ease of administration for both patients and caregivers, and greater compliance. The clinical literature has shown that a patient's subjective perception of the benefits of nebulization in symptom control has a positive impact on the patient's compliance with their prescribed medication.⁸⁴ In a related vein, patients have shown that they prefer nebulization and believe it to be more effective even when significant differences in lung function were not observed.⁸⁵

D. Nebulized formoterol enhances patient compliance by enabling less frequent dosing.

Development of a nebulized LABA for the treatment of COPD offers the advantage of less frequent dosing compared to currently approved nebulized treatments with short-acting beta agonists. The proposed number of daily doses for FHS is twice daily, which is one half of currently available nebulized short-acting beta agonist therapies for COPD. As discussed above, there is an inverse linear relationship between the number of daily doses and the rate of compliance.⁸⁶

Once FDA-approved, DEY's FFIS product will enable COPD patients to have access to a nebulized version of the long-acting beta agonist, formoterol. As discussed above, LABAs are a critical part of the treatment of COPD, and a nebulized form will allow access for those patients who are unable to use inhalers correctly.

In sum, DEY's FFIS product will enable simpler, less frequent nebulized dosing regimens for COPD, which in turn may help many patients achieve in better compliance rates.

E. Summary on formoterol.

DEY's FFIS administered twice daily by nebulization is well-tolerated and provides significant improvement in respiratory status and quality of life in patients with COPD. The primary advantage of FFIS is that it presents an alternate treatment option of formoterol fumarate to physicians and COPD patients and addresses the unmet medical need for a long-acting beta agonist delivered via nebulization. As a standard of care, nebulization is used easily and effectively, offers less technique-associated dosing errors compared to MDIs and DPIs, and may be a patient's preferred delivery mode. Development of nebulized formoterol fumarate also offers the advantage of less frequent dosing compared to currently approved nebulized treatments with short-acting beta agonists, which may contribute to higher treatment compliance rates. In sum, the nebulized presentation of formoterol will provide a safe and effective delivery option for COPD patients requiring long-acting maintenance bronchodilator therapy.

Conclusion

DEY appreciates this opportunity to provide comments on the NCA. DEY supports CMS' efforts to bring higher quality care to Medicare beneficiaries suffering from COPD. We perceive that the agency is giving careful thought to appropriate coverage for COPD treatments and inhalation therapies generally. DEY would welcome the opportunity to work with CMS to develop an inhalation therapy benefit that would ensure appropriate coverage for Medicare beneficiaries. Please do not hesitate to contact us if you would like to discuss such a benefit, or if you have any other questions about these comments.

Sincerely,



J. Melville Engle
President and CEO

cc: **Louis Jacques, M.D**
Steve Phurrough, M.D, M.P.A.

¹ We observe that the tracking sheet seems not to have been continuously present on the CMS Web site during the 30-day period preceding the deadline for public comments. We understand that this, too, has had the effect of impeding the public's ability to provide meaningful comments.

² Alternative course of action include making clarifications within the context of this same NCA, then extending the period for initial public comments or offering an additional opportunity for such comments. However, under either of these alternatives, we are concerned that the statutory timeframes applicable to NCAs might have the practical effect of limiting the period for agency deliberations. *See* Social Security Act §1862(1)(2), (3) (42 U.S.C. §1395y(1)(2), (3)).

³ "Denial of Medicare Payment for Compounded Drugs Produced in Violation of Federal Food, Drug, and Cosmetic Act," §50A.7, Medicare Benefit Policy Manual (CMS Pub. 100-02).

⁴ "Social Security Act §1862(a)(1)(A) (42 U.S.C. §1395y(a)(1)(A)).

⁵ Letter of Mark McClellan, M.D., Administrator, Centers for Medicare and Medicaid Services, to Honorable Charles E. Grassley, Chairman, Senate Committee on Finance (Aug. 22, 2006), <http://finance.senate.gov/press/Gpress/2005/prg082206c.pdf>, accessed Jan. 11, 2007 (hereinafter, "McClellan Letter").

⁶ Bulletin 20070109, "Nebulizers - Code Changes and Revised Billing Instructions," TriCenturion, Durable Medical Equipment Program Safeguard Contractor, Jurisdiction A/B (January 2007), http://www.tricenturion.com/content/Doc_View.cfm?type=cb&File=nebulizer%20drug%20codes%20jan%202007%2Edoc, accessed Jan. 11, 2007. The bulletin delineates the affected codes and associated code descriptions .

⁷ McClellan Letter.

⁸ In another context, CMS has noted that "Medicare claims data contain a wealth of information about clinical outcomes ..." http://www.cms.hhs.gov/DeterminationProcess/03_PCA.asp#TopOfPage, accessed Jan. 11, 2007.

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<http://www.cms.hhs.gov/DemoProjectsEvalRpts/MD/itemdetail.asp?filterType=dual.%20keyword&filterValue=inhalation&filterByDID=0&sortByDID=3&sortOrder=ascending&itemID=CMS1186903&intNumPerPage=10>, accessed Jan. 11, 2007 (hereinafter "Demonstration Project Web Posting"). *See also*, Fact Sheet, "Appropriate Payments, High-Quality Care for Beneficiaries Using Inhalation Drugs," Centers for Medicare and Medicaid Services (Nov. 2, 2005), <http://www.cms.hhs.gov/apps/media/press/factsheet.asp?Counter=1716&intNumPerPage=10&checkDate=&checkKey=2&srchType=&numDays=0&srchOpt=0&srchData=inhalation&keywordType=All&chkNewsType=6&intPage=&showAll=1&pYear=2005&desc=&cboOrder=date>, accessed Jan. 11, 2007.

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January 12, 2007

Francina Spencer
Lead Analyst, Center for Medicare and Medicaid Services
7500 Security Boulevard
Mailstop C1-09-06
Baltimore, MD 21244

Dear Ms. Spencer:

CMS has requested a National Coverage Analysis for Xopenex, an effective respiratory medication. CMS plans to determine whether Xopenex, when compared to its generic alternative, racemic albuterol, is a necessary treatment for patients with COPD. I am in my eleventh year practicing medicine, and I prefer Xopenex when prescribing medication for pulmonary treatment. Racemic albuterol is inconsistent in treating respiratory conditions - Xopenex is a safer bet.

If Xopenex is found to be an unnecessary treatment option, the reimbursement rates for Xopenex could be drastically reduced, thus removing the drug from the Medicare formulary. Once this occurs, Medicare beneficiaries across the country would no longer have access to this required pulmonary therapy.

It is important that Xopenex remains a viable, affordable option for doctors administering treatment for pulmonary conditions. Reduced rates for Xopenex would force Medicare recipients to switch respiratory drugs, and the transition from Xopenex to racemic albuterol could produce negative side-effects in many elderly patients. Please do what you can to preserve current rates. Your time is much appreciated.

Sincerely,
~~Sincerely,~~


Frank Tortorice, MD

Re: CAG-00354N

This medication and the equipment that delivers it to patients has proved effective in prolonging life and improving the quality of life for countless patients suffering from chronic obstructive pulmonary disease. It is of vital importance that it be fully funded. It is cruel and unnecessary to impose limitations on access to a specific medication based on cost rather than benefit to patients.

Gerard M. Turino, MD
Director, James P Mara Center for Lung Disease
and Director Emeritus, Department of Medicine
St Luke's-Roosevelt Hospital, New York NY
John H. Keating Jr Professor of Medicine (emeritus)
Columbia University College of Physicians and Surgeons, New York NY"

NCA Tracking Sheet for Nebulized Beta Adrenergic Agonist Therapy for Lung Diseases (CAG-00354N)

I tried to add a comment on this page and could not. I have COPD and feel that nebulizers are very necessary in treatment of my disease. I use Xopenex and Pulmicort. Using these two helps keep me out of the hospital
Thank you,
Jeanne Brinson

January 19, 2007

Herb Kuhn
Acting Deputy Administrator
Center for Medicare and Medicaid Services
200 Independence Avenue, SW
Suite 314 G
Hubert H. Humphrey Building
Washington, DC 20201

Dear Ms. Spencer.

As a family care specialist with a large number of elderly patients, I have some concerns about the National Coverage Analysis for Xopenex. As I understand it, CMS initiated this analysis to determine whether racemic albuterol is an adequate substitute for Xopenex. For this reason, I thought it urgent to convey some of the negative implications of such a finding, especially as they pertain to elderly patients who rely on Xopenex for treatment of Chronic Obstructive Pulmonary Disease (COPD).

For many of my elderly patients who have pulmonary and respiratory conditions, I often prescribe Xopenex as a part of the treatment plan. Most senior patients experience very positive results when using Xopenex. Most medical professionals will agree that albuterol is not equivalent to Xopenex. Due to the unique therapeutic properties of Xopenex, COPD patients experience fewer side-effects and shorter treatment durations than with the generic drug.

I am concerned that the results of the national analysis could threaten availability of Xopenex to elderly patients. It seems quite possible that a reduction of Medicare reimbursement payments for the drug could occur, which means many seniors would not receive the medication they truly need. The care that doctors across the country have prescribed for their patients may be interrupted or completely eliminated due to financial constraints brought on by this analysis. .

Any reductions in Medicare rates will have detrimental consequences toward the health of many elderly pulmonary patients. Thank you for your time and concern of this urgent issue.

Sincerely,

Sincerely,

Basil Hamblin

Basil Hamblin

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LATHAM-WATKINS LLP

January 19, 2007

VIA ELECTRONIC MAIL AND FEDERAL EXPRESS

Steve E. Phurrough, M.D.
Director, Coverage Analysis Group
Centers for Medicare & Medicaid Services
Office of Clinical Standards & Quality
7500 Security Boulevard
Mail Stop C1-09-06
Baltimore, MD 21224

Re: Comments on National Coverage Analysis of Nebulized Beta Adrenergic Agonist Therapy for Lung Diseases (CAG-00354N)

Dear Dr. Phurrough:

We are writing on behalf of our client, Rotech Healthcare Inc. ("Rotech"), to comment on the National Coverage Analysis to determine when treatment with a nebulized beta adrenergic agonist is reasonable and necessary for Medicare beneficiaries with chronic obstructive pulmonary disease ("COPD") (hereinafter, "the NCA"). Rotech appreciates this opportunity to present its comments to the Centers for Medicare and Medicaid Services' Coverage Analysis Group ("CAG"). We note at the outset of these comments that nebulized beta adrenergic agonist therapy for Medicare beneficiaries with COPD has been well established and accepted by the medical community, vastly improving the quality of life of many patients with COPD and other respiratory disorders. Further, the Agency's intended focus for the NCA is unclear from the NCA tracking sheet. Because currently pending is the Durable Medical Equipment Program Safeguard Contractors' ("DME PSCs") draft local coverage determinations {"LCDs"}-which question the clinical efficacy of two commonly-prescribed inhalation drugs: levalbuterol (Xopenex®) and the manufactured combination of albuterol and ipratropium bromide {DuoNeb®}-Rotech focuses its comments on these two drugs. The Company also presents comments on formoterol, and highlights the substantial clinical evidence to support the medical necessity and critical differences among all three Part B inhalation drugs.

Rotech is one of the largest suppliers of home medical equipment in the United States, focusing on equipment and services for older patients with breathing disorders, such as COPD, obstructive sleep apnea and other cardiopulmonary disorders. This includes providing nebulizer

equipment and inhalation therapy medications to Medicare beneficiaries. Rotech dispenses inhalation medication through its pharmacy, Pulmo-Dose, Inc., a wholly-owned subsidiary that services patients in 49 states. Pulmo-Dose dispenses both commercially-manufactured products and compounded preparations, as prescribed by physicians.

Rotech believes that to best serve the Medicare population, the NCA should reflect both the DME PSCs' current coverage policies and expand coverage to other clinically proven beta adrenergic drugs, as described further below.

Summary of Comments

With this letter, we are submitting comments in each of the following areas:

(1) **Nebulizers are a Critical Mode of Delivery for Many Patients:** For many patients who are unable to effectively use other delivery devices (e.g., metered dose inhalers ("MDIs") and dry powder inhalers), nebulizers are the only mode of delivery for such patients to receive their life-saving medications.

(2) **Xopenex and DuoNeb are Critically Different From Other Beta Adrenergic Agonist Drugs:** Xopenex and DuoNeb are by no means clinically the same as albuterol and albuterol/ipratropium bromide (as separate components), nor are they "deluxe" versions of those drugs. Currently-available albuterol and ipratropium are not "standard" versions of these brand name drugs. *Rather, they are entirely different drugs with different clinical effects, safety profiles and costs,* and the Agency's NCD should distinguish these clinically important drugs from their components.

(3) **Formoterol Should Be Covered:** There is substantial clinical evidence to support the medical necessity and clinical superiority of formoterol for elderly patients suffering from chronic obstructive pulmonary disease, asthma and reversible obstructive airways disease over similar drugs in its class. Therefore, the Agency should take this opportunity to include coverage for formoterol, which currently is excluded under Medicare Part B contractor policies.

(4) **A Least Costly Alternative Policy Is Inappropriate for Xopenex and DuoNeb:** The DME PSCs have proposed to revise existing regional coverage policies to use a least costly alternative ("LCA") policy for coverage of Xopenex and DuoNeb. This policy was proposed in draft LCDs published in March 24, 2006. However, because cost effectiveness is not a factor the Centers for Medicare and Medicaid Services ("CMS") considers in making NCDs, the Agency has historically declined to implement an LCA policy at the national level. Here, because the application of an LCA policy in the context of inhalation drugs is clinically inappropriate, CMS should find at the national level that the adoption of an LCA also would be improper at the local level for Xopenex and DuoNeb.

Nebulizers Are A Critical Mode Of Delivery For Many Patients

CMS has recognized the importance of nebulizers and Medicare's continued coverage of inhalation drugs generally. This longstanding policy is supported by a body of clinical evidence underscoring the vital importance of nebulized drugs. Even when CMS began providing coverage for inhalation drugs administered through metered dose inhalers ("MDIs") under the Part D benefit,¹ the Agency underscored that the new coverage would not supplant the existing Part B drug benefit:

We believe *expansion* of Medicare coverage of inhalation drugs to include MDIs under Medicare Part D will provide additional options for treatment and positively impact access to care.... [W]e recognize that nebulizers are required by many beneficiaries because of their individual circumstances. We believe that physicians will choose the treatment option that best meets a beneficiary's needs, and *both* nebulizers and MDIs will play an important role in the Medicare program in the years to come.²

Importantly, Rotech has found that patients' physical and/or cognitive inability to use other devices correctly—despite the amount of time spent by health care professionals educating these patients—makes the available mode of nebulized administration critical to effective treatment.³ Nebulized drugs for these patients maximize drug delivery,⁴ minimize the risk of medication errors and increase patient compliance.⁵ All of these factors ultimately minimize costs to the Medicare program because of fewer emergency room visits, shorter hospital stays and fewer dollars spent on wasted medication.⁶

The challenges associated with MDIs for physically and cognitively challenged patients are further exacerbated with the release of newer inhaler designs, each with a unique set of instructions, sometimes contradictory to other MDIs. Nebulizer therapy is optimal because its mode of delivery is largely independent of patient technique. While the patient and/or caregiver must correctly assemble the inhaler, incorrect assembly is apparent when aerosolized mist is absent. Unlike MDI therapy, nebulizer therapy can be effectively used with infants, mentally impaired or even comatose patients who cannot follow instructions.

Xopenex and DuoNeb are Critically Different From Other Beta Adrenergic Agonist Drugs

Substantial clinical evidence shows that Xopenex and DuoNeb are different in many significant ways from similar drugs of the same class. A discussion of the key differences is instructive to support their continued Medicare coverage.

Xopenex/Levalbuterol Versus Albuterol Alone

Levalbuterol is an FDA-approved drug indicated for treatment or prevention of bronchospasm in adults, adolescents and children 6 years of age or older with reversible obstructive airway disease (including asthma, COPD, cystic fibrosis, and chronic bronchitis). It is a single source drug with no generic equivalents. Levalbuterol is a distinct chemical entity and not a reformulation of albuterol; levalbuterol comprises only one stereoisomer-(R)-albuterol, a bronchodilator that binds to beta-adrenergic receptors on the smooth muscles of the patient's airway, causing the muscles to relax. Albuterol, on the other hand, is a combination of both (R) and (S)-albuterol isomers. (S)-albuterol has a number of unique pharmacologic effects, many of which can act in an anti-therapeutic fashion, sometimes causing pro-inflammatory activity. Because levalbuterol does not combine with an (S)-albuterol isomer, the use of levalbuterol does not produce detrimental side effects sometimes associated with the use of albuterol.

Based upon the clinical data available, Rotech believes there are a number of identified differences in the safety, efficacy and cost effectiveness of the two drugs, as follows:

- *Levalbuterol (in a 1.25 mg dosage) offers greater efficacy and longer duration.* Levalbuterol in dosages of 125 mg has been clinically proven to result in greater bronchodilation than 25 mg of albuterol. In addition, the bronchodilatory effect of levalbuterol was found to last several hours longer than the lesser effect of albuterol.⁷ One

study found that patients taking levalbuterol experienced continued improvements over time in their breathing ability (as measured according to forced expiratory volume, or FEV₁, in the first second of the patient's forcibly exhaled breath). Patients taking albuterol reached a plateau in their response over the same time period.⁸ As a result, a greater proportion of patients using levalbuterol reported a better quality of life than those using albuterol.⁹

- *Levalbuterol is cost effective.* Levalbuterol does not need to be administered as often as albuterol. Several studies demonstrate that levalbuterol reduces the number of hospital admissions and shortens hospital stays.¹⁰ One study found that hospitalized patients needed fewer total treatments when levalbuterol was used.¹¹ In addition, even costs associated with other medications and procedures may decrease if levalbuterol is used. Scientific evidence supports that fewer rescue or ancillary therapies are needed with levalbuterol,¹² reducing the number of shifts that required extra respiratory therapists in one study.¹³

- *Xopenex offers dosing flexibility and fewer side effects.* Levalbuterol has been clinically proven to be safe and effective in both 0.31 mg and 0.63 mg dosages.¹⁴ A number of studies confirm that patients taking levalbuterol experienced fewer side effects, including changes in heart rate, serum glucose and serum potassium levels, than those taking albuterol.¹⁵ Given the wealth of scientific materials demonstrating these important differences in efficacy, clinical benefit, safety, dosing, and overall cost of Xopenex in comparison to albuterol, the two drugs should not be equated to each other. The NCD should reflect the clinical differences between the two products since they are distinct products with different clinical effects, safety profiles and costs.

DuoNeb Versus Albuterol and Ipratropium Bromide Separately

DuoNeb is an FDA-approved drug indicated for treatment of bronchospasm associated with COPD for patients who require more than one bronchodilator. It combines albuterol and ipratropium bromide in a single vial. Like Xopenex, it is a single source drug with no generic equivalents. Albuterol and ipratropium can also be compounded or dispensed separately. Neither of these formulations are the same as DuoNeb. Rotech believes that there are a number of differences in the products, which are borne out by clinical studies, as follows:

- *DuoNeb is more cost effective than separately administered albuterol and ipratropium.* The use of DuoNeb is associated with a lower rate of exacerbations in COPD. The result is lower total treatment costs and improved cost-effectiveness.¹⁶ Patients who use DuoNeb have a significantly lower risk of emergency department use or hospitalizations, lower mean monthly health care charges and shorter hospital stays.¹⁷ As a result, DuoNeb use leads to a decreased financial burden over and above the effect observed from separate administration of the two component agents,¹⁸ and also has the benefit of increased compliance.¹⁹

- *DuoNeb results in higher patient adherence to treatment regimens, effectively decreasing overall morbidity.* It is common sense that patients are more likely to adhere to treatment plans that are convenient and easy to follow. As the volume of solution is reduced from 5.5 ml with separate vials (2.5 ml ipratropium and 3 ml of albuterol) to 3 ml with DuoNeb, treatment time with DuoNeb is approximately half that of the drugs taken separately (5 to 7 minutes for DuoNeb, in contrast to 10 to 15 minutes for individual vials).²⁰ This significantly shorter treatment time is more convenient for

patients, which in turn, increases compliance. Because DuoNeb is a single vial and can be more quickly administered, patients are more likely to follow the treatment plan when using DuoNeb than when using the two drugs separately.²¹

Rotech believes that most patients take DuoNeb 4 times per day (with some as many as 6 times per day), which makes ease of administration and the time to which the patient is tied to the nebulizer significant in determining whether patients will follow the treatment regimen. Patients who have limited dexterity or experience pain associated with opening vials (*e.g.*, due to arthritic hands) would fare better with the single DuoNeb vial. Also, Rotech believes patients are less likely to ration medications to save money when there is only a single medication.

- *DuoNeb is more effective in treating moderate to severe COPD.* The combination therapy results in increased bronchodilation in comparison to either therapy alone.²² DuoNeb improves bronchodilation 24 percent more than albuterol alone and 37 percent more than ipratropium alone.²³ Common COPD symptoms, including shortness of breath, cough, fatigue and production of mucus, are reduced to a greater degree with DuoNeb than with either therapy alone.²⁴ Patients also experience better sleep (as measured by such indicia as improvements in mean nocturnal SpO₂, in patients' perception of sleep quality, and in REM sleep time, as well as increases in lung volume and airflow, and decreased awakenings per hour of sleep).²⁵
- *DuoNeb 's beneficial effects last longer.* DuoNeb also has a longer lasting effect than albuterol or ipratropium alone.²⁶ Some researchers believe that delivery of the two agents from one device results in better co-deposition and, hence, increased opportunity for synergistic interaction.²⁷
- *DuoNeb allows patients to take a lower cumulative dose of albuterol and ipratropium resulting in equivalent or improved side effects.* Patients with COPD are particularly vulnerable to the adverse effects of drugs. 8 Combining drugs that result in synergistic interaction, above and beyond the separate administration of the individual components may lead to a better side effect profile,²⁹ resulting in improved health status and increased compliance.
- *There is a lower risk of patient medication errors with DuoNeb.* The U.S. Pharmacopeia ("USP") ranks albuterol 2nd and ipratropium 15th for medication errors; in contrast, USP ranks DuoNeb 41st.³⁰ If a patient has multiple vials that look nearly identical (as do vials of albuterol and ipratropium), s/he may inadvertently open and use two vials of the same drug. This is clearly not a concern for patients who use only one vial of DuoNeb at any given time.

For the reasons described above, Rotech believes that Xopenex and DuoNeb have sufficient and significant clinical differences than albuterol or ipratropium alone, or as separate vials of albuterol and ipratropium. Given the many clinical benefits of these drugs, it is important to preserve physicians' ability to prescribe Xopenex or DuoNeb, as appropriate, for their patients- and to be assured that, once prescribed, patients will be able to obtain the products.

Rotech dispenses these inhalation drugs based on a physician's order. The physician is in the best position to understand the patient's medical condition and specific treatment needs. When a physician prescribes Xopenex or DuoNeb, s/he does so after performing an

individualized assessment of the patient. Rotech is concerned that any coverage policy that does not reflect these critical differences may inadvertently but effectively ignore the physician's professional medical judgment—a result that the Agency should avoid.

In addition, restrictions to coverage will put a serious roadblock in the way of beneficiaries for whom these drugs are essential. CMS should retain current coverage and avoid compromising the availability of these life-sustaining medications.

Notably, pharmacists may not be able to substitute albuterol or ipratropium when a physician orders Xopenex or DuoNeb. According to the FDA "Orange Book," the official Federal compendium of approved drugs with therapeutic equivalents, neither Xopenex nor DuoNeb has any therapeutic equivalents.³¹ Many states do not permit generic drugs to be substituted for brand name drugs with no therapeutic equivalents. Often, these states rely on the FDA "Orange Book" in determining whether a particular drug is therapeutically equivalent.³² Thus, in many circumstances, pharmacists would be unable to substitute the less costly drugs for Xopenex and DuoNeb. If the Agency restricted coverage of Xopenex and DuoNeb (and only covered albuterol and ipratropium), the only recourse available to and possible for pharmacists is to cease offering Xopenex and DuoNeb. These drugs will not be available to beneficiaries because pharmacies will be unable to afford to provide them. The Agency should not effectively "down-code" Xopenex and DuoNeb to drugs that are not medically appropriate substitutes.

Formoterol Should Be Covered

Formoterol is an FDA-approved drug indicated for the maintenance treatment of asthma, prevention of bronchospasm in reversible obstructive airways disease, acute prevention of exercise-induced bronchospasm when administered on an occasional, as needed basis and maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema.³³ It is within the same class of drugs (B₂ agonist) as salmeterol (Serevent®), salbutamol and albuterol.

Rotech believes that there are a number of differences in safety, efficacy and cost-effectiveness between formoterol and other B₂ agonist drugs (both short- and long-acting), which are borne out by clinical studies, as follows:

- *Current COPD guidelines recommend long-acting beta agonists over short-acting beta agonists for the routine management of stable moderate to severe COPD. **There is a rich body of data** from randomized clinical trials that show that regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators.³⁴ While short-acting bronchodilators are seen as the cornerstone of treatment as relief or "rescue" medication, current guidelines recommend long-acting beta agonists as maintenance therapy in patients with moderate to severe disease.³⁵*

- *Formoterol is more effective, has longer duration and has no reduction in clinical efficacy over time, as compared to shorter acting P2 agonist drugs like albuterol and salbutamol. Formoterol results in significantly greater improvements in patients' overall quality of life, mean total symptom scores, objective measures of lung function and clinical efficacy end points, including morning premedication peak expiratory flow, as compared to salbutamol³⁶ and albuterol,³⁷ making formoterol a much more efficacious treatment for patients with asthma and other obstructive airways diseases. It leads to fewer adverse symptoms including less nocturnal symptoms and sleep disturbances.³⁸ Finally, long-term studies have shown that there is no reduction in its clinical efficacy*

and, therefore, no development of tolerance to formoterol, compared to shorter-acting drugs.³⁹

- *Formoterol is clinically safer than other long-acting P2 agonist drugs such as salmeterol.* Formoterol has a faster onset of action and is more efficacious as compared to salmeterol.⁴⁰ Because of salmeterol's pharmacokinetic properties, salmeterol may partially block the effect of short-acting B₂ agonist drugs typically used as rescue medication (such as albuterol), potentially leading to catastrophic consequences for patients suffering from acute exacerbations of asthma or other obstructive airways diseases requiring rescue medication.⁴¹

- *Formoterol combines the best properties of long and short-acting P2 agonist drugs.* Formoterol exhibits a similar rapid onset of action of such short-acting drugs as albuterol and the longer duration of long-acting drugs such as salmeterol,⁴² with little or no increase in adverse side effects. Thus, formoterol, with its fast- and long-acting profile, is effective when used both as maintenance and as-needed therapy for patients with reversible obstructive airways disease.⁴³

- *Dry powder formoterol nebulized in a saline solution can offer patients additional clinical benefits.* Some patients, particularly Medicare beneficiaries, may be unable to perform effective inhalatory maneuvers due to such factors as age or difficulty in breathing and a nebulized administration of formoterol may offer a beneficial therapeutic option in such instances.⁴⁴

- *Formoterol is cost-effective and will save Medicare money in the long run.* The increased clinical efficacy of formoterol leads to less rescue⁴⁵ and maintenance medication usage and reduced healthcare resource utilization.⁴⁶ Formoterol may reduce the number of acute exacerbations, leading to a reduced rate of readmissions, emergency room use and subsequent hospitalizations due to more effective medical management of the patient's disease.

For the reasons described above, Rotech believes that formoterol is shown to be a clinically meaningful P₂ agonist drug and warrants coverage by Medicare. It is imperative that beneficiaries be given the ability to use formoterol for better management of their diseases. For many patients, the medication offers superior clinical benefits to other covered drugs.

A Least Costly Alternative Policy Is Inappropriate for Xopenex and DuoNeb

According to the Agency's NCD guidance document: "Cost effectiveness is not a factor CMS considers in making NCDs. In other words, the cost of a particular technology is not relevant in the determination of whether the technology improves health outcomes or should be covered for the Medicare population through an NCD."⁴⁷ The Agency, however, gives its contractors discretion to establish LCDs that include the use of a least costly alternative policy to determine drug pricing⁴⁸ (and the pricing for other covered items or services).⁴⁹ These are payment provisions, however, and do not belong in a coverage policy, particularly an NCD.

CMS has declined to revise its historical position on the least costly alternative policy. Recently, in response to the Office of Inspector General's recommendation to CMS that the Agency "encourage all Medicare carriers" to apply an LCA policy to Lupron (a gonadotropin-releasing hormone agonist used to treat several conditions such as fibroids, prostate cancer,

endometriosis and central precocious puberty), the Agency stated: "CMS determines national guidelines and criteria that must be followed by all of its contractors in creating [LCDs, but] ... *CMS generally does not influence the application of these guidelines in any specific circumstance.*"⁵⁰ CMS further stated that any action to encourage an LCA policy would disrupt the "longstanding ability of *contractors* to apply an LCA policy under section 1862(a)(1)(A) of the [Social Security] Act."⁵¹

Perhaps most critically, even if CMS decided to act contrary to its past practices and consider an LCA policy in the context of a national coverage determination or otherwise encourage its application, implementation of such a policy in the context of inhalation drugs is inappropriate. Section 1862(a)(1)(A) of the Social Security Act⁵² states that Medicare excludes coverage for "items or services that are not reasonable and necessary for diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." If two items or services are clinically comparable, or if there is no demonstrable clinical difference between them, then the additional cost of the more expensive item or service arguably would not be attributable to a feature that is medically reasonable and necessary and, thus, might be construed as non-covered by Medicare.

In the case of drugs, an LCA policy is only appropriate for clinically *equivalent* products, such as among different branded products of the *same* active drug.⁵³ It is therefore inappropriate to apply this type of LCA analysis to Xopenex and *DuoNeb* -- *i.e.*, make payment at the rate for albuterol and a combination of the rates for albuterol and ipratropium bromide, respectively because of the important clinical differences addressed above.

The LCA policy that payment for a product is to be based on the rate for another product⁵⁴ is to be used only where it is the least costly alternative treatment that could replace the billed product and that meets the Medicare beneficiary's individual medical needs. The Medicare Benefit Policy Manual states:

Where a claim is filed for equipment containing features of an aesthetic nature or features of a medical nature which are not required by the patient's condition or where there exists a reasonably feasible and medically appropriate alternative pattern of care which is less costly than the equipment furnished, the amount payable is based on the rate for the equipment or alternative treatment which meets the patient's medical needs.⁵⁵

An LCA policy in a coverage decision here would require blanket "down-coding" without heed to whether the alternative nebulized drug is actually suitable for the patient's condition. Notably, the circumstances here also are wholly different from the situation where Medicare contractors are permitted to down-code to least costly alternatives for items of durable medical equipment in order to ensure that Medicare does not pay for "bells and whistles" that are not needed by the patient.⁵⁶ The Medicare Claims Processing Manual explains that:

Additional expenses for "deluxe" features, or items that are rented or purchased for aesthetic reasons or added convenience, do not meet the reasonableness test. Thus, where a service or item is medically necessary and covered under the Medicare program, and the patient wishes to obtain such deluxe features, the payment is based upon the payment amount for the kind of service or item normally used to meet the intended purpose (*i.e.*, the standard item.). Usually this is the least costly item.⁵⁷

Here, an LCA policy would fail to recognize the critical clinical differences between the brand name drugs and the less costly drugs to which their payment rates would be linked. Because of the costs incurred to manufacture these products, pharmacies would be required to cease providing Xopenex and DuoNeb to Medicare beneficiaries since the LCA policy would result in unsustainable payment rates. Therefore, CMS should underscore in a national coverage determination the clinical significance of these drugs and the need to continue to make them available to Medicare patients.

With respect to an LCA policy for DuoNeb, such a policy would also constitute unbundling-an activity that CMS has long discouraged and prohibited.⁵⁸ That is, under the LCA policy, pricing for DuoNeb is based on the HCPCS codes for its two component drug parts, albuterol and ipratropium. There is a good reason for the government's longstanding prohibition against unbundling: resources attributable to providing component parts of a drug (or other item) are not the same as the drug (or other item) itself, and payment levels reflect this distinction. Suppliers are not permitted to take advantage of pricing differentials to bill for a drug (or other item) using its components rather than the drug (or other item) itself. The logic is equally true when applied here. It stands established policy on its head to proceed with such a policy simply because the economics weigh in the government's favor.

CMS should ensure that its policies and those of its contractors avoid the blurring of coverage and payment. Perhaps most critically, under the Medicare statute, as of January 1, 2005, payment rates for Part B inhalation drugs dispensed through nebulizers are based on the average sales price ("ASP") methodology. The statutory formula distinguishes between single and multiple source drugs. ⁹ For single source drugs, such as Xopenex and DuoNeb, rates are set at 106% of the lesser of ASP and wholesale acquisition cost.⁶⁰ Generally, ASP is the drug manufacturer's ASP for a drug for a calendar quarter to all purchasers (with certain exclusions and including most discounts given by the manufacturer).⁶¹ An LCA policy for Xopenex and DuoNeb, however, would set payment rates for these brand name drugs based on the payment rates for two multiple source drugs-albuterol and ipratropium. This methodology, therefore, runs counter to the congressionally-prescribed payment formula.

Thank you for your attention to our comments. We welcome any questions that this letter may raise regarding the NCA to determine when treatment with a nebulized beta adrenergic agonist is reasonable and necessary for Medicare beneficiaries with COPD, and look forward to speaking with you on the NCA. In the interim, should you have any questions or comments, we can be reached at 202-637-2200.

Truly yours,



Stuart S. Kurlander
Esther R. Scherb
Of LATHAM & WATKINS LLP

Enclosure (Reference List and Abstracts)

Cc:

Rotech Healthcare Inc.
Betty C. Pang, Latham & Watkins LLP

¹ Medicare Part B provides for the coverage of drugs that require administration by the use of covered durable medical equipment ("DME"), such as a nebulizer (administered in the home). There is no explicit statutory coverage of the drugs in the instance of nebulized drugs, but rather, they are considered a supply necessary for the DME to perform its function. *See* 42 U.S.C. § 1395x(n); *see also* 42 C.F.R. 414.202. In contrast, drugs delivered with a metered dose inhaler or other non-nebulized administration are covered under Medicare Part D. In turn, for Medicare Part B coverage, a coverage determination (local and/or national) could be made to evaluate medical necessity and whether the drug fits in a Part B benefit category (for inhalation drugs, as an item of DME). Part D coverage is determined by different standards; specific coverage may also largely depend on the particular prescription drug plan's formulary and/or the plan sponsor's decision to cover the drug on an exception basis. *See* 42 U.S.C. § 1395w-102.

² 70 Fed. Reg. 70116, 70232 (November 21, 2005) (emphasis added).

³ *See, e.g.*, Dolovich MB et al. "Device Selection and Outcomes for Aerosol Therapy: Evidence-based Guidelines." *Chest* 2005; 127:335-371; Jones JS et al. "MDI: DoEmergency Health Care Providers Know What to Teach?" *Ann Emerg Med* 1995; 26:308-311; Lindgren S et al. "Clinical Consequences of Inadequate Inhalation Technique in Asthma Therapy." *Eur J Respir Dis* 1987; 70:93-98; Shrestha M et al. "MDI Technique of Patients in an Urban ED: Prevalence of Incorrect Technique and Attempt at Education." *Am J Emerg Med* 1996; 14:380-384; Liard R et al. "Misuse of Pressurized MDI by Asthmatic Patients Treated in French Private Practice." *Rev Epidemiol Sante Publique* 1995; 43:242-249; Johnson DH, Robart P. "Inhaler Technique of Outpatients in the Home." *Respir Care* 2000; 45(10):1182-1187; Gray SL et al. "Characteristics Predicting Incorrect MDI Technique in Older Subjects." *Arch Intern Med* 1996; 156:984-988; Skaer TL et al. "MDI Technique and Quality of Life with Airways Disease: Assessing the Value of the Vitalograph in Educational Intervention." *J Int Med Res* 1996; 24:369-375; Pounsford JC. "Nebulizers for the Elderly." *Thorax* 1997; 52(Suppl):S53-S55; Allen SC. "Competence Thresholds for the Use of Inhalers in People with Dementia." *Age Ageing* 1997; 26:83-86; Fink ill et al. "Problems with Inhaler Use." *Respir Care* 2005; 50(10):1360-1374.

⁴ *See, e.g.*, Oliver S, Rees Pl. "Inhaler Use in Chronic Obstructive Pulmonary Disease." *Int J Clin Pract* 1997 Oct; 51(7):443-5.

⁵ *See* Rand CS et al. "Metered Dose Inhaler Adherence in a Clinical Trial." *Am Rev Respir Dis* 1992; 146(6):1559-64; Milgrom H et al. "Noncompliance and Treatment Failure in Children with Asthma." *J Allergy and Immunol* 1996; 98(6):1051-1057. Rotech's internal data, gathered from the company's patient education program and monthly reorder calls, shows that over 60 percent are compliant with their inhalation drug regimen when administered via a nebulizer.

⁶ *See, e.g.*, Fink JB et al. "Problems with Inhaler Use." *Respir Care* 2005; 50(10):1360-1374.

⁷ Nelson et al. "Improved Bronchodilation with Levalbuterol Compared with Racemic Albuterol in Patients with Asthma." *J. Allergy Clin. Immunol.* 1998 December; 102(6):943-952; Pleskow et al. "Pairwise Comparison of Levalbuterol Versus Racemic Albuterol in the Treatment of Moderate-to-severe Asthma." *Allergy & Asthma Proceedings* 2004 November-December; 25(6):429-436.

⁸ Nowak R. et al. "Levalbuterol Compared with Racemic Albuterol in the Treatment of Acute Asthma: Results of a Pilot Study." *Am. J. Emerg. Med.* 2004; 22(1):29-36; *see also* Nowak R., et al. "Levalbuterol (LEV) vs. Racemic Albuterol (RAC) in Acute Severe Asthma: A Prospective Trial." *Am. J. Respir. Crit. Care Med.* 2004; 169:A310 (Abstract).

⁹ Donohue et al., *Poster Presented at the Annual Meeting of the American College of Chest Physicians 2005*; Montreal, Quebec.

¹⁰ Truitt et al. "Levalbuterol Compared to Racemic Albuterol: Efficacy and Outcomes in Patients Hospitalized with COPD or Asthma." *Chest* 2003; 123(1):128-135; Schreck et al. "Comparison of Racemic Albuterol and Levalbuterol in the Treatment of Acute Asthma in the ED." *Am. J. Emerg. Med.* 2005; 23(7):842-847; Carl et al. "Comparison of Racemic Albuterol and Levalbuterol for Treatment of Acute

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¹⁵ Nelson et al. "Improved Bronchodilation with Levalbuterol Compared with Racemic Albuterol in Patients with Asthma." *J. Allergy Clin. Immunol.* 1998; 102(6):943-952; Milgrom et al. "Low-dose Levalbuterol in Children with Asthma: Safety and Efficacy in Comparison with Placebo and Racemic Albuterol." *J. Allergy Clin. Immunol.* 2001; 108(6):938-945; Gittlen et al. "Improved Reversibility with Levalbuterol Versus Racemic Albuterol in Obstructive Lung Disease." *Chest* 2001; 120(suppl):163S (Abstract); Portnoy et al. "Patients and Physicians Prefer Levalbuterol Over Racemic Albuterol: A Comparison Preference Study." *Ann. Allergy Asthma Immunol.* 2001; 86:102 (Abstract); Ohar et al. "Physicians and Patients Prefer Levalbuterol to Racemic Albuterol." *Ann. Of Allergy, Asthma & Immunol.* 2002; 88:132 (Abstract); Vaickus et al. "Impact of Decreasing Doses of Racemic Albuterol and Levalbuterol on Efficacy: A Pooled Analysis." *J. Allergy Clin. Immunol.* 2002; 109:S707 (Abstract); Handley DA et al. "Dose Response Evaluation of Levalbuterol Versus Racemic Albuterol in Patients with Asthma." *J Asthma* 2000; 37(4):319-27; O'Alonzo GE. "Levalbuterol in the Treatment of Patients with Asthma and capo." *JAOA* 2004; 104:288-293.

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³⁴ See Global Initiative for Chronic Obstructive Lung Disease, "Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease 2006," available at <http://www.goldcopd.com/Guidelineitem.asp?11=2&12=1&intId=989>. See also Dahl R, Greefhorst LA, Nowak D, Nonikov V, Byrne AM, Thomson MH, et al. "Inhaled Formoterol Dry Powder Versus Ipratropium Bromide in Chronic Obstructive Pulmonary Disease." *Am J Respir Crit Care Med* 2001; 164(5):778-84.

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⁴⁷ See Centers for Medicare and Medicaid Services, "Factors CMS Considers in Opening a National Coverage Determination," available at http://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=6.

⁴⁸ See Medicare Claims Processing Manual (CMS Pub. 100-04), Chapt. 17, § 20.2 (Single Drug Pricer); see also Medicare Benefit Policy Manual (CMS Pub. 100-02), Chapt. 15, § 110.1 (Definition of Durable Medical Equipment) ("[W]here there exists a reasonably feasible and medically appropriate alternative

pattern of care which is less costly than the equipment furnished, the amount payable is based on the rate for the equipment or alternative treatment which meets the patient's medical needs"). *See, e.g.*, Wheatlands Administrative Services, Inc., "LCD for Lupron/Zoladex (L928 I)," *available at* http://www.cms.hhs.gov/mcd/viewlcd.asp?lcd_id=9281&lcd_version=9&basket=led%3A9281%3A9%3ALupron%2FZoladex%3ACarrier%3AWheatlands-Administrative+.Services%7C%7C-line%2E+%2800650%29%3A.

⁴⁹ *See, e.g.*, Tricenturion, "LCD for Power Mobility Devices (L21271)," *available at* http://www.cms.hhs.gov/mcd/viewlcd.asp?lcd_id=Q1271&lcd_version=i8&show=all.

⁵⁰ Department of Health and Human Services, Office of Inspector General, "Medicare Reimbursement for Lupron," January 2004 OEI-03-03-00250, Appendix, Letter to Dara Corrigan, Office of Inspector General, from CMS Administrator Thomas A. Scully dated November 15, 2003, page 2, *available at* http://www.medicarerxguide.com/MDRG/2006/OIG_Lupron.pdf.

⁵¹ 70 Fed. Reg. 70116, 70243 (November 21, 2005).

⁵² *See* Section 1862(a)(1)(A) of the Social Security Act, *codified as* 42 U.S.C. § 1395y(a)(1)(A).

⁵³ *See* Medicare Payment Advisory Commission, "January 2007 Report to the Congress: Impact of Changes in Medicare Payments for Part B Drugs," *available at* http://www.medpac.gov/publications/congressional_reports/Jan07_PartB_mandated_report.pdf?CFID=1441184&CFTOKEN=30531942.

⁵⁴ *See* 42 U.S.C. § 1395m(a).

⁵⁵ Medicare Benefit Policy Manual (CMS Pub. 100-02), Chapt. 15, § 110.1.

⁵⁶ *See* 42 U.S.C. § 1395m(a)(19).

⁵⁷ Medicare Claims Processing Manual (CMS Pub. 100-04), Chapt. 20, § 90. Additionally, unlike deluxe items of DME, beneficiaries cannot elect to pay out-of-pocket for more expensive drugs.

⁵⁸ *See, e.g.*, Program Integrity Manual (CMS Pub. 100-08), Chapt. 4, § 4.2.1 (listing "unbundling" as an example of Medicare fraud).

⁵⁹ A multiple source drug is that for which, for a calendar quarter, there are 2 or more drug products that are rated as therapeutically equivalent by the FDA, are deemed pharmaceutically equivalent and bioequivalent by the FDA, and are sold or marketed in the U.S. in that quarter. In contrast, a single source drug is defined

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Age Ageing. 1997 Mar; 26(2):83-6.

Competence thresholds for the use of inhalers in people with dementia.

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METHODS: the ability to learn three inhaler techniques of increasing levels of complexity was studied in 50 normal and demented inhaler-naive elderly people (mean age 81 years) with stable 10-point mini-mental test scores (MTS). There were 10 subjects in each of the following groups: MTS 8-10 (non-demented), MTS 7 (borderline), MTS 6 (mild dementia), MTS 5 and MTS 4 (2 moderate dementia groups). The techniques were taught on one day and reassessed on the following day on consecutive days in ascending order of complexity. **RESULTS:** those with an MTS of 4 were unable to learn any of the techniques, while all the non-demented people could learn all three techniques. For the five-stage technique (standard metered dose inhaler) the 0% threshold (i.e. when none of the subjects was able to learn) was MTS 6, the 50% threshold (at least half but not all could learn) MTS 7 and the 100% threshold (all could learn) MTS 8. For the four-stage technique (inhaler with large spacer) the 0% threshold was MTS 5, the 50% threshold MTS 6 and the 100% threshold MTS 8. For the three-stage technique (inspiration-triggered inhaler) the 0% threshold was MTS 4, the 50% threshold MTS 5 and the 100% threshold MTS 7. **CONCLUSIONS:** MTS can be used to determine the likelihood of a mild or moderately demented patient being able to learn a multiple-stage inhaler technique.

Chest. 2005 Jan;127(1):335-7L

Device selection and outcomes of aerosol therapy: Evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology.

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BACKGROUND: The proliferation of inhaler devices has resulted in a confusing number of choices for clinicians who are selecting a delivery device for aerosol therapy. There are advantages and disadvantages associated with each device category. Evidence-based guidelines for the selection of the appropriate aerosol delivery device in specific clinical settings are needed. **AIM:** (1) To compare the efficacy and adverse effects of treatment using nebulizers vs pressurized metered-dose inhalers (MDIs) with or without a spacer/holding chamber vs dry powder inhalers (DPIs) as delivery systems for beta-agonists, anticholinergic agents, and corticosteroids for several commonly encountered clinical settings and patient populations, and (2) to provide recommendations to clinicians to aid them in selecting a particular aerosol delivery device for their patients.

METHODS: A systematic review of pertinent randomized, controlled clinical trials (RCTs) was undertaken using MEDLINE, EmBase, and the Cochrane Library databases. A broad search strategy was chosen, combining terms related to aerosol devices or drugs with the diseases of interest in various patient groups and clinical settings. Only RCTs in which the same drug was administered with different devices were included. RCTs (394 trials) assessing inhaled corticosteroid, beta2-agonist, and anticholinergic agents delivered by an MDI, an MDI with a spacer/holding chamber, a nebulizer, or a DPI were identified for the years 1982 to 2001. A total of 254 outcomes were tabulated. Of the 131 studies that met the eligibility criteria, only 59 (primarily those that tested beta2-agonists) proved to have useable data.

RESULTS: None of the pooled metaanalyses showed a significant difference between devices in any efficacy outcome in any patient group for each of the clinical settings that was investigated. The adverse effects that were reported were minimal and were related to the increased drug dose that was delivered. Each of the delivery devices provided similar outcomes in patients using the correct technique for inhalation.

CONCLUSIONS: Devices used for the delivery of bronchodilators and steroids can be equally efficacious. When selecting an aerosol delivery device for patients with asthma and COPD, the following should be considered: device/drug availability; clinical setting; patient age and the ability to use the selected device correctly; device use with multiple medications; cost and reimbursement; drug administration time; convenience in both outpatient and inpatient settings; and physician and patient preference.

Respir Care. 2005 Oct; 50(10):1360-74; discussion 1374-5.

Problems with inhaler use: a call for improved clinician and patient education.

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Patient education is a critical factor in the use and misuse of medication inhalers. Inhalers represent advanced technology that is considered so easy to use that many patients and clinicians do not receive adequate training in their use. Between 28% and 68% of patients do not use metered-dose inhalers or powder inhalers well enough to benefit from the prescribed medication, and 39-67% of nurses, doctors, and respiratory therapists are unable to adequately describe or perform critical steps for using inhalers.

Of an estimated 25 billion dollars spent for inhalers annually, 5-7 billion dollars is wasted because of inhaler misuse. Reimbursement and teaching strategies to improve patient education could substantially reduce these wasted resources. Problems with inhaler use, the cost of inhalers, and myths associated with inhalers are reviewed, with recommendations for strategies and techniques to better educate patients in inhaler use.

Characteristics predicting incorrect metered-dose inhaler technique in older subjects

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OBJECTIVE: To determine whether cognitive status, hand strength, and demographic variables are predictive of correct use of metered-dose inhalers by older subjects.

METHODS: Clinic patients (n =29) and healthy volunteers (n =42) older than 50 years with no previous or limited metered-dose inhaler use were enrolled. After cognitive (Mini-Mental State Examination) and hand strength assessments, subjects received extensive instruction in proper metered-dose inhaler technique. Technique was independently assessed by two evaluators immediately after instruction and 1 week later. Correct technique was defined as (1) activating the canister in the first half of inhalation, (2) continuing to inhale slowly and deeply, and (3) holding breath at full inspiration (5 seconds). Data for the two subject groups were pooled for analyses.

RESULTS: The mean age of the subjects was 69.7 years. Forty subjects (56%) demonstrated correct metered-dose inhaler technique at 1 week. Logistic regression showed that hand strength measurement (odds ratio, 0.68; 95% confidence interval, 0.55 to 0.84), Mini-Mental State Examination score less than 24 (odds ratio, 3.66; 95% confidence interval, 1.07 to 12.4), and male gender (odds ratio, 5.01; 95% confidence interval, 1.07 to 23.5) were significant predictors of incorrect inhaler use. Correct use of the metered-dose inhaler was unrelated to age, education, or subject status.

CONCLUSIONS: Clinicians should consider cognitive status and hand strength when metered-dose inhaler therapy is initiated for an older adult. Patients with cognitive impairment and hand strength deficits may require more extensive training, frequent follow-up, or alternative dosage forms.

Respir Care. Oct; 45(10):1182-7.

Inhaler technique of outpatients in the home.

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OBJECTIVE: Assess the role of evaluation, instruction, and use of spacers by patients, using metered dose inhalers (MDIs) in the home.

PATIENTS AND SETTING: Patients (age 64 +/- 15 y [mean +/- standard deviation]) receiving home visits by respiratory care practitioners for oxygen therapy had their inhaler technique checked.

INTERVENTIONS AND MEASUREMENTS: A detailed acceptable/unacceptable check-off list was used with 172 patients to evaluate inhaler technique. Patients with poor technique were given instruction and their technique was reassessed. A subgroup of 43 patients was reevaluated on up to 3 visits.

RESULTS: Only 18% of patients using MDIs without spacers were rated acceptable with the detailed check list. Instruction improved inhaler technique, but few patients with initially poor technique without spacers developed fully acceptable technique. Improvements made immediately following instruction were lost when patients were reevaluated months later. Few patients received spacers after they were recommended. Technique was markedly better with spacers. Most patients (76%) had initially proper technique with spacers, and most who had poor technique could learn and retain proper technique.

CONCLUSIONS: Improper inhaler technique without spacers is very common among patients evaluated at home, and the majority of patients were unable to learn and retain proper technique. Most patients would benefit from using spacers with their inhalers. =33 for first and second. =26 for third. PRC =functional residual capacity. RV =residual volume. TLC =total lung capacity.

Ann Emerg Med.1995 Sep;26(3):308-11.

Metered-dose inhalers: do emergency health care providers know what to teach?

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STUDY OBJECTIVE: To evaluate the ability of emergency health care providers and patients to demonstrate the proper use of metered-dose inhalers (MDIs).

DESIGN: Prospective cross-sectional survey.

SETTING: Five Midwestern community teaching hospitals.

PARTICIPANTS: One hundred eighty-five health care providers, comprising emergency medicine house staff (n =60), attending emergency physicians (n =50), and ED nurses (n =75). Also recruited were 100 consecutive ED patients with clinical history of asthma being treated with at least one MDI for more than 3 months.

INTERVENTIONS: We surveyed patients and health care providers to assess their knowledge of and ability to use a conventional MDI. The subject's technique of using a placebo inhaler was graded by a trained observer using a checklist of six essential steps.

RESULTS: Forty-one percent (76 of 185) of health care providers and 49% (49 of 100) of ED asthma patients performed at least five steps correctly (P =.24). There were no significant differences in performance scores among the emergency medicine house staff (42 %), attending emergency physicians (34 %), and ED nurses (45 %). Only 15%of all health care providers and 17%of asthma patients were able to describe how to estimate the amount of medicine left in the canister.

CONCLUSION: These results suggest that many patients use MDIs improperly. Emergency physicians, house staff, and nurses responsible for instructing patients in optimal inhaler use may lack even rudimentary skills with these devices.

Rev Epidemiol Sante Publique; 1995; 43(3):242-9.

Misuse of pressurized metered dose inhalers by asthmatic patients treated in French private practice.

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Although metered dose inhalers (MDIs) are widely used to treat asthma, clinical studies suggest that misuse is frequent. We studied the frequency of, and factors related to, misuse of MDIs in asthmatic patients of French private practice. 264 chest specialists or general practitioners completed questionnaires including characteristics of patients and asthma, technique in using inhalers and previous instruction, for three consecutive asthmatics aged >6 years and currently using MDIs: 668 adults (mean age 47.8 years +/- 18.5, 51.8% males) and 100 children (mean age 11.5 years +/- 2.1, 72.0% males) were included. Adequate technique (deep inspiration synchronized with inhaler activation, followed by holding breath for 5 seconds) was used by 33.2% of adults and 26.0% of children; optimal technique (same, plus shaking the inhaler before use and activating it only once) was used by 22.1 % of adults and 20.0% of children. The main factor related to misuse of MDIs was absence of previous instruction. However, only 26.5% of instructed adults and 22.1 % of instructed children used the optimal technique. Misuse of MDIs is a public health problem and instruction is unlikely to solve it. The use of different types of devices, like dry powder breath-actuated inhalers should be encouraged.

Eur J Respir Dis. 1987 Feb; 70(2):93-8.

Clinical consequences of inadequate inhalation technique in asthma therapy.

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The FEV₁-increase after inhalation of a beta 2-stimulant metered-dose aerosol was studied in 23 patients treated by specialists. The effect of their spontaneous inhalation technique was compared with that of controlled inhalation, which was optimised by means of a device controlling the breathing pattern and release of the metered-dose aerosol. This allowed quantitative assessment of the loss of bronchodilatation caused by the spontaneous inhalation technique. Thirteen patients who were observed to make inhalation errors showed a significant loss of bronchodilatation (30%), whereas ten patients who were observed to make no inhalation errors showed an insignificant loss of bronchodilatation (13%). It is concluded that when a metered-dose aerosol is used in general clinical practice there is a considerable loss of potential efficacy.

J Allergy Clin Immunol. 1996 Dec;98(6 Pt 1):1051-7.

Noncompliance and treatment failure in children with asthma.

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BACKGROUND: Accurate and reliable information about children's use of inhaled medications is needed because of the growing reliance on these drugs in the treatment of asthma and the excessive morbidity and mortality attributable to this disease.

OBJECTIVE: This study was designed to evaluate the adherence of children with asthma to regimens of inhaled corticosteroids and beta-agonists.

METHODS: Data collected electronically by metered-dose inhaler monitors were compared with data recorded by patients on traditional diary cards. A volunteer sample of 24 children, between 8 and 12 years old, who had asthma for which they were receiving both inhaled corticosteroids and beta-agonists, participated over a 13-week period. Each child was accompanied by a parent to all study visits. The main outcome measures were the use of medication as reported by diary card entries and recorded by electronic monitoring and disease exacerbation, as indicated by requirement for oral corticosteroids.

RESULTS: The median use of inhaled corticosteroids reported by patients on their diaries was 95.4%, whereas the median actual use was 58.4%. More than 90% of patients exaggerated their use of inhaled steroids, and diary entries of even the least compliant subjects reflected a high level of adherence. The children who experienced exacerbation of disease sufficient to require a burst of oral corticosteroids differed markedly from the others in their adherence to prescribed therapy as recorded by the electronic monitors. The median compliance with inhaled corticosteroids was 13.7% for those who experienced exacerbations and 68.2% for those who did not.

CONCLUSIONS: Electronic monitoring demonstrated much lower adherence to prescribed therapy than was reported by patients on diary cards. Low rates of compliance with prescribed inhaled corticosteroids were associated with exacerbation of disease. Poor control of asthma should alert the physician to the possibility of noncompliance.

Int J Clin Pract. 1997 Oct; 51(7):443-5.

Inhaler use in chronic obstructive pulmonary disease.

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Inhaler technique is a common problem, particularly in the elderly. We have assessed the ability to use seven common inhaler devices in 20 patients with chronic obstructive pulmonary disease (COPD). Techniques were taught in a standard fashion in random order and assessed immediately and one hour later by two observers. Fourteen patients had a fault that would result in no drug delivery at some time during the study, and such a fault occurred at some point for each inhaler device. These faults were most common with the diskhaler. Accuhaler, autohaler and turbohaler scored highest and diskhaler lowest. Overall scores declined by one hour after instruction. Patients ranked the metered dose inhaler and accuhaler highest for ease of use and preference. These results show that it is useful to have a small range of devices for patients with COPD and that it is important to review inhaler technique regularly.

Nebulisers for the elderly

J C Pounsford

Asthma mortality in England and Wales is slowly rising with about 2000 deaths per annum. If these figures are examined with respect to age, corrected for population size, mortality in patients over the age of 65 is rising significantly and deaths in those aged over 80 is increasing exponentially. Some "asthma deaths" may be explained by changing patterns in death certification with chronic obstructive pulmonary disease (COPD) being certified as asthma. There is a need to ensure that older patients are diagnosed accurately and treated in the most appropriate manner.

Nebulisers in the elderly are largely used to administer inhaled bronchodilators to patients with bronchial asthma and COPD with reversibility. There is a lack of published data on the efficacy and use of nebulisers in this age group, and clinical decisions tend to be based on results from studies in younger patients. Some studies in COPD have included patients up to age of 75 but the results have rarely been examined with respect to age.

This paper will consider some of the special features of asthma in the elderly which might modify nebuliser use. In addition, some of the risks of high dose B agonists and anticholinergic drugs will be discussed.

Use of metered dose inhalers

One of the most challenging problems in managing elderly patients with asthma is the delivery of treatment to the lungs. Armitage and Williams showed that age was a major factor when assessing whether patients were able to use a metered dose inhaler correctly, with patients under the age of 65 doing significantly better than older patients. The older patients were significantly less likely to learn an inhaler technique than the younger patients. The study also showed that many metered dose inhalers currently available in the UK require considerable strength in the index finger and thumb to activate aerosol release. The force required could not be achieved by a large proportion of elderly patients studied. Buckley assessed inhaler technique in relation to age in patients with asthma and COPD. Those with COPD were older and less likely to be able to use an inhaler correctly than asthmatic patients, but age was not an independent factor in predicting inability to use an inhaler.

Age and strength might predict problems with competence in inhaler technique in the general asthmatic population, but in an elderly cohort of patients age becomes much less important than cognitive function. In a group of patients aged over 75 years who had previously been taught to use their inhalers correctly, cognitive function or memory, as assessed by the Hodgkinson's mini mental test, was the best predictor of inability to use a metered dose inhaler. In a further study a breath activated and metered dose inhaler was shown to be the only inhaler that some patients with moderately severe memory loss could use. As 20% of patients over the age of 80 are significantly cognitively impaired, assessment of cognitive function becomes an important aspect in the management of patients in whom inhaled therapy is being considered. For patients who are cognitively impaired a nebulised bronchodilator would seem a useful option, but a well trained carer might be able to administer bronchodilators satisfactorily with a metered dose inhaler and a spacer or a dry powder inhaler.

The relative paucity of evidence to show that nebulisers are better than metered dose inhalers, particularly when used in high dose with spacers, necessitates all types of metered dose inhalers and dry powder inhalers being available and considered for each patient. The only inhaler device which has been shown to give a significant benefit to the elderly and patients with poor inhaler technique is the Autohaler." Many patients inhale well from the Autohaler but they have considerable difficulty in spring loading the device. In a number of uncontrolled studies the Turbohaler is popular with patients although elderly patients frequently complain that they are unaware whether they are receiving the drug when they inhale from the device. The risk of inhalation from an empty Turbohaler is not inconsiderable.

Having exhausted trials of various inhaler devices including instructing patients and, if necessary, carers on the use of large spacer devices, a nebuliser needs to be considered if patients are not adequately treated. Special consideration must be given to the drugs and the dosage that are conventionally used in nebulisers.

β agonists

The incidence of ischaemic heart disease rises with age and this may be asymptomatic. Care should be exercised when administering a nebulised β agonist to a patient with known ischaemic heart disease and the first dose should be given in the lung function laboratory, ideally with an ECG recording before drug administration. The incidence of dysrhythmias following nebulised β agonists is well recognized and has been reported to be as high as 65% in patients with acute bronchial asthma. No significant difference in the incidence of dysrhythmia was seen in a group of patients who were studied in the acute and convalescent phase of their illness, but the risk of a serious dysrhythmia was significantly increased in those who had had a previous myocardial infarction.

Hypokalaemia is a recognised complication of nebulised β agonist therapy and baseline potassium levels should be measured, particularly if patients are on a diuretic or have a poor dietary intake. The combination of theophylline with β agonists has been reported to increase myocardial damage in some animal studies and the hypokalaemic effects of nebulised β agonists are increased in patients receiving oral theophylline.

A further complication of treatment with high dose β agonists is hypoxaemia which may be responsible for increasing asthma mortality. In a group of patients with asthma and COPD, some of whom were hypoxic and hypercapnoeic, no serious fall in oxygen levels (P_{O_2}) occurred when patients received salbutamol for 15 minutes from a nebuliser driven by air. A proportion of patients who were hypercapnoeic developed further rises in carbon dioxide (P_{CO_2}) when the nebuliser was driven by oxygen. All patients returned to their pre-nebuliser (baseline) blood gas levels shortly after drug administration. In a similar study in an older group of 22 subjects with severe COPD (mean FEV₁, 0.54-0.87 l) nebulised terbutaline (4 mg) driven by air caused a rise in P_{O_2} , even in those patients who were hypoxic. Transcutaneous P_{CO_2} fell in the normoxic and hypoxic group and the changes in oxygen saturation were attributed to mouthpiece induced hyperventilation. The conclusion from both these studies was that nebulisers could be driven by air.

Anticholinergic drugs

Ipratropium bromide and oxitropium bromide have a good safety profile. There are no long term studies of ipratropium in the elderly, but short term studies in normal subjects and patients with normal angle glaucoma have shown that intraocular pressure, pupil diameter, and accommodation are not affected by ipratropium bromide given in doses up to four times that which is recommended. Prolonged pupillary dilatation can occur if the drug is sprayed directly into the

eye, and particular care needs to be taken if the drug is given through a nebuliser when the face mask needs to fit well. An alternative is to use the nebuliser with a mouthpiece attached to a T piece. There is no evidence that inhaled ipratropium given in the short term has any effect on urinary flow in men aged 50-70, but long term data on high dose nebulised ipratropium is required.

Treatment

The choice of bronchodilator in the elderly poses additional clinical problems. Two studies have suggested that the bronchodilator response to inhaled β agonists declines with age, but the studies could be criticised as lung volumes were not adequately corrected for age. Connolly, however, has shown that the return to baseline FEV₁ following methacholine challenge and subsequent β agonist administration is considerably impaired in elderly patients with asthma compared with younger patients.

This evidence, and the relative lack of side effects from inhaled anticholinergics, suggests that anticholinergic drugs should always be considered in a nebuliser assessment of an elderly patient. The overlap between bronchial asthma and COPD is less easy to define in the elderly and the proven efficacy of anti-anticholinergic bronchodilators in COPD would further justify their use. There is no evidence to support a trial of anticholinergic drugs before β agonists or vice versa, and both should always be tried.

Assessment:

The lack of published data in the elderly will necessitate a degree of pragmatism in deciding who should be issued with a nebuliser. Our preference is to measure FEV₁ and FVC in the laboratory after bronchodilators have been given by metered dose inhaler and nebuliser on separate occasions. This is followed by a four week assessment period when peak expiratory flow rate is measured four times a day. The patient uses high dose inhaled bronchodilators with an inhaler device for the first two weeks, and a nebuliser for the second two. Peak flow recordings and symptoms are then discussed with the patient before it is decided whether to supply him or her with a nebuliser.

There is increasing evidence that the bronchodilator response to anticholinergic agents is less age dependent than the response to β agonists and, on this evidence, we always recommend a combination of a β agonist and ipratropium bromide in our elderly patients.

In conclusion, nebuliser treatment for the elderly needs further evaluation and should be reserved for those patients who are symptomatic despite treatment with conventional metered dose inhalers or dry powder inhalers which they are using ineffectively but to the best of their ability. After first checking potassium levels the patient should be given a nebuliser trial for at least two weeks. It is our clinical practice to assess peak flow and symptoms before prescribing nebulisers and we routinely use combined β agonist and anticholinergic therapy.

The potential risks of cardiac side effects of high dose inhaled β agonists need to be evaluated in well controlled clinical trials.

Am Rev RespirDis. 1992 Dec;146 (6):1559-64.

Metered-dose inhaler adherence in a clinical trial.

Rand CS, Wise RA, Nides M, Simmons MS, Bleecker ER, Kusek JW, Li VC, Tashkin DP.

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We studied patterns of inhaler usage in a sample of participants from two centers in the Lung Health Study clinical trial. The inhaler, containing either ipratropium bromide or a placebo, was prescribed to be taken as two inhalations three times daily. For 4 months we recorded adherence by both self-report (n =95) and canister weight change (n =70). We compared these results with data obtained from a microprocessor monitoring device, the Nebulizer Chronolog (NC), which records the date and time of each inhaler actuation. Seventy-three percent of the participants reported using the inhaler an average of three times daily; however, NC data showed that only 15% of the participants actually used the inhaler an average of 2.5 or more times per day. Canister weight overestimated adherence because only 62%of the NC sets contained the prescribed two actuations. Fourteen percent showed a pattern of actuation of their inhalers more than 100 times in a 3-h interval. We interpret this usage pattern to reflect deliberate emptying of inhalers to appear to be in good compliance with the prescribed program. We conclude that self-report and weighing of inhaler canisters overestimate adherence to the prescribed regimens. Furthermore, a substantial number of monitored inhaler users appear to deliberately dump their medication prior to follow-up visits.

Am J Emerg Med. 1996 Jul;14 (4):380-4.

Metered-dose inhaler technique of patients in an urban ED: prevalence of incorrect technique and attempt at education.

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The metered-dose inhaler (MDI) techniques of 125 asthma patients who presented to a county hospital emergency department (ED) were evaluated. Correct technique was divided into 7 steps. Twenty-one percent of the patients performed all 7 steps correctly. Mean number of steps \pm SD performed correctly was 4.8 \pm 1.7. Verbal individualized instruction was used to improve the technique of patients whose technique was less than perfect. The instruction required a mean \pm SD of 8.3 \pm 5.8 minutes (range, 0 to 30) for all 7 steps to be done correctly at least once. All patients were able to perform all steps correctly after instruction. The amount of time required for teaching was proportional to the number of steps performed incorrectly. The Vitalograph Aerosol Inhalation Monitor was used to verify correct patient technique and as a teaching aid with variable success. Education in proper use of the MDI is important in the overall care of the asthma patient; however, instruction requires a definite time commitment and may not be feasible for all patients in a busy ED. For some patients, alternatives that require less lengthy instruction, such as the use of breath-actuated devices, spacers, and reservoirs, may be required.

J Int MedRes. 1996 Jul-Aug;24 (4):369-75.

Metered-dose inhaler technique and quality of life with airways disease: assessing the value of the Vitalograph in educational intervention.

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The efficacy of delivering medicines by metered-dose inhaler (MDI) is well established, and the patient's technique with MDIs is related directly to achieving the desired clinical outcome. The present study was designed to assess and improve MDI technique by using a Vitalograph Aerosol Inhalation Monitor (VAIM) in an airways disease education programme. Baseline measurements were made immediately prior to educational intervention incorporating feedback from a VAIM unit. At 6 weeks' follow-up, MDI technique was found to have regressed to the sub-optimal measures recorded at baseline prior to educational intervention. However, patients reported a significant improvement in physical function between baseline and follow-up as measured by the Rand 36-Item Health Survey (SF-36), Version 1.0. The results reinforce the need for a longitudinal educational programme for patients prescribed medications delivered by MDI. The VAIM unit provided health educators and patients with both a visual and a quantitative assessment of patients' MDI technique, and was thus of positive value as part of the intervention process.

LEVALBUTEROL

J Pediatr. 2003 Dec;143 (6):731-6.

Comparison of racemic albuterol and levalbuterol for treatment of acute asthma.

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OBJECTIVE: To determine whether levalbuterol resulted in fewer hospital admissions than racemic albuterol when used for treatment of acute asthma. Study design A randomized, double-blind, controlled trial was conducted in the emergency department (ED) and inpatient asthma care unit of an urban tertiary children's hospital. Children age 1 to 18 years (n=482) provided a total of 547 enrollments. Patients received a nebulized solution of either 2.5 mg racemic albuterol or 1.25 mg levalbuterol every 20 minutes (maximum six doses). Patients admitted to the asthma care unit were treated in a standardized fashion by using the same blinded drug assigned in the ED. Hospitalization rate was the primary outcome.

RESULTS: Hospitalization rate was significantly lower in the levalbuterol group (36%) than in the racemic albuterol group (45 %, P=.02). The adjusted relative risk of admission in the racemic group compared with the levalbuterol group was 1.25 (95% confidence interval, 1.01-1.57). Hospital length of stay was not significantly shorter in the levalbuterol group (levalbuterol, 44.9 hours; racemic albuterol, 50.3 hours; P=.63). No significant adverse events occurred in either group.

CONCLUSIONS: Substituting levalbuterol for racemic albuterol in the ED management of acute asthma significantly reduced the number of hospitalizations.

Levalbuterol in the Treatment of Patients With Asthma and Chronic Obstructive Lung Disease

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Effective asthma control requires long-term (anti-inflammatory) controller medications for patients with mild-persistent to severe-persistent disease, and quick-relief bronchodilator medication for all patients with asthma to control intermittent symptoms of cough, wheeze, and bronchoconstriction, as well as acute exacerbations. For patients with chronic obstructive pulmonary disease, quick-relief and long-acting bronchodilators are primarily used in the maintenance and treatment of associated symptoms, including shortness of breath. For many years, the most widely used bronchodilator has been racemic (R, S)-albuterol, a short-acting β_2 adrenergic agonist, commonly dispensed as an inhaled aerosol or solution.

Until the introduction of levalbuterol inhalation solution (Xopenex) in 1999, all marketed forms of albuterol (including Ventolin and Proventil brands) were racemic mixtures composed of a 1:1 ratio of (R)- and (S)-stereoisomers. Administered as a proportionally equivalent nebulized dose, levalbuterol [(R)-albuterol] provides greater bronchodilation than racemic albuterol and, in the appropriate clinical setting, offers the possibility for improving clinical outcomes in patients with asthma and other obstructive airway diseases. Additionally, levalbuterol can be given at lower doses than racemic albuterol to provide comparable bronchodilation, with the potential for reduced β -mediated adverse effects in adults and children. Only since the past decade has the technology to separate stereoisomers become available, and thus the biologic activities of the albuterol stereoisomers had not been established.

Binding studies have demonstrated that (R)-albuterol binds to the β_2 -adrenergic receptor with a high affinity, whereas (S)-albuterol binds with 100-fold less affinity than (R)-albuterol. Other evaluations have suggested that (R)-albuterol possesses the bronchodilatory, bronchoprotective, and ciliary-stimulatory properties of racemic albuterol, while (S)-albuterol does not contribute beneficially to the therapeutic effects of the racemate and was originally assumed to be inert. However, preclinical evaluations have shown that (S)-albuterol has effects that work in opposition to (R)-albuterol and may diminish the therapeutic effects of (R)-albuterol.

A COMPARISON OF THE USE OF LEVALBUTEROL COMPARED TO RACEMIC ALBUTEROL IN THE PULMONARY STEPDOWN POPULATION

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HYPOTHESIS: Racemic Albuterol consists of both an R-isomer and an S-isomer. The R-isomer is responsible for bronchodilation. The S-isomer is not inert, but rather may exaggerate airway reactivity and cause loss of airway control. Levalbuterol is a new preparation that contains only the R-isomer and has a longer duration than racemic albuterol. We hypothesized that routine use of levalbuterol administered TID would require fewer overall as well as PRN treatments than racemic albuterol administered QID.

METHOD: The study design was a three month observational period using levalbuterol TID + pro instead of racemic albuterol + pm as the standard beta agonist bronchodilator therapy on our pulmonary step-down unit. The same three month period during the previous year when racemic albuterol was the standard beta agonist bronchodilator therapy was used as a historical control period. Total and pm treatments/patient were calculated during both periods and compared using unpaired T tests.

RESULTS: The total number of treatments decreased from 3835 during the control period to 2613 when Levalbuterol was used (3.5 treatments per patient day and 2.8 treatments per patient day respectively - $p < 0.05$). The number of PRN treatments declined from 540 during the control period (Racemic Albuterol) to 375 during the levalbuterol period (0.5 pm treatments and 0.4 pm treatments per patient day respectively $p < 0.05$).

CONCLUSION: Levalbuterol 1.25 mg delivered on a TID + PRN basis results in fewer PRN treatments per patient day as compared to the Administration of Racemic Albuterol 2.5 mg QID +PRN.

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IMPROVED REVERSIBILITY WITH LEVALBUTEROL VERSUS RACEMIC ALBUTEROL IN OBSTRUCTIVE LUNG DISEASE. Stanford D Gittlen¹, Kendyl Schaefer² and Raymond J Claus². ¹Respiratory Department, Wanninster Hospital, Warminster, PA, United States; and ²Medical Operations, Sepracor, Marlborough, MA, United States

Purpose: Levalbuterol (Lev) is the (R)-isomer of racemic albuterol (Rac). This study compared treatment with Lev, free of (S)-albuterol, with Rac in reversal of bronchoconstriction in obstructive lung disease (OLD).

Methods: Patients admitted with OLD (COPD or asthma, n=42) randomly received Lev 1.25 mg or Rac 2.5 mg one day, followed by the opposite treatment 24hrs later. PFTs were completed pre and 15 min post-bronchodilator. Heart rate and subjective assessment of tremor and shortness of breath (SOB) were collected.

Results: Treatment with Lev resulted in numerically greater improvements in lung function vs Rac for all patients and for the COPD subset (table). Improvements vs Rac ranged from 37-68%. Rac increased post-dose HR (mean HR 92, range 64-133) compared to Lev (mean HR 87, range 61-113). The mean change in HR following Rac was significantly increased from pre-dose, and was significantly greater than that seen with Lev. Side effects of tremor and SOB were lower after Lev (5% and 7%, respectively) vs Rac (7 % and 15%).

Conclusion: Lev 1.25 mg produced larger changes in pulmonary function than Rac 2.5 mg in hospitalized patients with OLD with fewer beta-medicated side effects, indicating a better therapeutic index for the single isomer product.

Clinical Implications: These data support the use of Lev as front-line bronchodilator therapy in hospitalized patients with OLD, as Lev appears to offer somewhat better efficacy with fewer side effects.

	All Patients		COPD	
	Lev 1.25mg	Rac 2.5mg	Lev 1.25mg	Rac 2.5mg
%chg FEV ₁	19± 32	11 ±20	21±34	13 ± 16
%chg FVC	16±28	10± 17	18±31	12 ±15
% chg FEF ₂₅₋₇₅	36±55	31 ±47	33±34	32±36
Mean chg HR	2.3 bpm	8.8 bpm*	1.6 bpm	7.8 bpm
Range chg HR	-13 to 18	-5 to 29	-13 to 13	-5 to 28
·p<0.001 vs baseline; p<0.001 vs Lev				
mean ± SD reported				

Ginlen SD, Schaefer K., Claus R. Improved Reversibility With Levalbuterol Versus Racemic Albuterol in Obstructive Lung Disease. CHEST, 2001.

LEVALBUTEROL & RACEMIC ALBUTEROL: A COMPARISON STUDY

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Background: Patients with severe onset of respiratory illness often go to the Emergency Department (ED) for immediate medical attention. This study evaluated a comparison in the clinical outcomes of aerosolized Levalbuterol and Racemic Albuterol on that population of patients.

Methods: Data was collected on 456 patients during a 3-month study. All adult patients presenting with onset of severe onset of respiratory illness were included in this study. All patients received aerosolized medication with the Airlife sidestream high-efficiency nebulizer. It was decided to target 2 specific outcomes: 1) Number of hospital admissions for patients each medication, 2) Number and frequency of treatments for patients receiving each medication.

Results	# receiving Levalbuterol	# receiving Racemic Albuterol
ED patients treated	299	157
Avg. # of treatments In ED	3	5
Avg. LOS in ED	1.75 hrs	2.8 hrs
Hospital admissions	29 (10 %)	98 (60%)
Avg. # of treatments In Hospital	7	16
Avg. LOS in Hospital	2.25 days	3.2 days

Conclusion: In this study, patients treated with Levalbuterol Demonstrated significant decrease in total treatment times in both the ED and hospital, hospital admits, and LOS for both the ED and Hospital as compared to Racemic. Levalbuterol nebulization appears To make a vast impact on both clinical and financial outcomes.

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**LEVALBUTEROL (LEV) AFFORDS SUPERIOR HEALTH AND COST BENEFIT
OVER RACEMIC ALBUTEROL (RAC) IN THE EMERGENCY DEPARTMENT (ED).**

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RAC, the most common β_2 -agonist bronchodilator used in the treatment of acute asthma exacerbation, is comprised of 50:50 mixture of (R)- and (S)-albuterol; however, only (R) albuterol (levsalbuterol) provides bronchodilatory activity. This study compared LEV and RAC for the treatment of acute bronchoconstriction from primary asthma 1 in the ED. Patients (≥ 12 years of age) were administered either RAC (n=30) or LEV (n=24). Atrovent® was administered concomitantly with the first dose of either β_2 -agonist but then only as subjectively necessary. Mean initial PEF (L/min) and FEV₁ (L) were measured in a subset of RAC (n=16) and LEV (n=13) patients and were similar between the treatment groups (PEF, 209.2 vs. 208.6; FEV₁, 1.21 vs. 1.17). Pulmonary function improved in patients administered either β_2 -agonist, however, the extent of improvement was greater among LEV patients compared to RAC patients (% Δ PEF, 68% for LEV vs. 46% for RAC; % Δ FEV₁, 70% for LEV vs. 34% for RAC). Greater bronchodilation was achieved with lower total amounts of LEV (3 mg/patient) compared to RAC (11.5 mg/patient). In addition, total Atrovent® amounts utilized were ~3-fold lower in LEV patients (0.45 mg) compared to RAC patients (1.5 mg). LEV patients experienced decreased heart and respiratory rate suggesting resolution of hypoxia and reduced anxiety. In contrast, RAC patients showed increased heart rate and less of a decrease in respiratory rate. Also, decreased incidence of β_2 -agonist-associated side effects (tremor, nervousness, tachycardia, dizziness, nausea, cough and headache) were observed in LEV patients compared to RAC patients. Twenty percent of RAC patients were admitted to the hospital subsequent to ED therapy, while 12% of LEV patients were admitted. Length of hospital stay was 35 hours for RAC patients and 23 hours for LEV patients. Despite the higher cost of LEV (\$1.54/unit dose) compared to RAC (\$0.30/2.5 mg unit dose; \$0.60/5.0 mg unit dose) and Atrovent® (\$1.12/0.5 mg unit dose); the total cost of bronchodilator therapy between the two groups was similar (\$4.89 and \$4.23 for LEV and RAC, respectively). This resulted from fewer LEV and Atrovent® administrations necessary to achieve bronchodilation. These data suggest that LEV, compared to RAC, is a clinically superior bronchodilator, decreases β_2 mediated side effects, improves clinical outcomes, and provides cost efficient asthma management in the ED.

Haider D. Levalbuterol (Lev) Affords Superior Health and Cost Benefit Over Racemic Albuterol (RAC) in the Emergency Department. AARC, 2001.

J Asthma. 2000 Jun;37 (4):319-27.

Dose-response evaluation of levalbuterol versus racemic albuterol in patients with asthma.

Handley DA, Tinkelman D, Noonan M, Rollins TE, Snider ME, Caron J. Sepracor Inc., Marlborough, Massachusetts 01752, USA. dhandley@sepracor.com

Albuterol, in all marketed forms, is sold as a racemate, composed of a 50:50 mixture of (R)- and (S)-isomers. Racemic albuterol and the single isomer version (R)-albuterol (levalbuterol) were compared in a randomized, double-blind, dose-ranging five-way crossover study in patients (n =20) with mild persistent to moderate persistent asthma. Placebo, racemic albuterol (2.50 mg), or levalbuterol (0.31,0.63, or 1.25 mg) were delivered as single, nebulized doses to 5 male and 15 female nonsmoking patients with asthma aged 18-50 years. Serial pulmonary function was assessed at 15-min intervals and mean time to onset of activity and duration of improvement of forced expiratory volume in 1 sec (FEV1) were measured. In addition, blood chemistries, electrocardiogram (ECG) readings, and patient subjective assessment of adverse symptoms were recorded. Levalbuterol was found to provide significant bronchodilatory activity and was well tolerated. Levalbuterol 1.25 mg provided the greatest increase and duration in FEV1 improvement, whereas racemic albuterol (2.50 mg) and levalbuterol 0.63 mg provided comparable effects. The lower doses of levalbuterol were associated with a less marked effect on heart rate and potassium than racemic albuterol or high-dose levalbuterol. These data suggest that 0.63 mg levalbuterol provides bronchodilation equivalent to 2.50 mg racemic albuterol with less beta-mediated side effects.

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Conversion from Racemic Albuterol to Levalbuterol, Jim L. Johnson, Charles D. Gibson, and Jim F. Cox, St. Mary's Hospital, Rogers, Arkansas

Rationale: Levalbuterol was shown to be effective when dosed q8 h without compromising lung function or causing an increase in PRN rescue med use.

Objective: To compare outcomes when racemic albuterol was replaced by levalbuterol.

Methods: Standard racemic albuterol 2.5 mg q4 h was converted to levalbuterol 0.63 mg or 125 mg q8 h in pediatric or adult patients with asthma or COPD. The number of beta-agonist and ipratropium bromide treatments administered was monitored daily using RT Dept Daily Treatment Forms and corroborated from pharmacy billing records. The number of extra RTs worked per shift and RT time was monitored by recording number of therapists required to fill shifts where workload exceeded capacity of scheduled RTs. The same time periods were compared over two consecutive years.

Results: The number of nebulized beta agonist treatments decreased by 14% with the switch to levalbuterol. Use of ipratropium bromide decreased by 97%. PRN rescue treatments decreased from 13% of the total nebs administered with racemic albuterol to 2.5% of the total with levalbuterol. The number of additional therapists that were required to handle the workload decreased from 12 shifts in the albuterol period to 1 shift in the levalbuterol period and we avoided hiring an additional 4 RTs.

Conclusions: Changing to levalbuterol resulted in improvements in drug delivery and decreased nebulized drug treatments.

Implications: Use of levalbuterol may result in cost savings and more efficient use of hospital resources.

Johnson JL, Gibson CD, Cox JF. Conversion from racemic albuterol to levalbuterol. *Int Pharm Abs* 2003; 38:P-12. [Abstract]

J Allergy Clin Immunol. 2001 Dec;108 (6):938-45.

Low-dose levalbuterol in children with asthma: safety and efficacy in comparison with placebo and racemic albuterol.

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BACKGROUND: Racemic albuterol (RAC) is an equal mixture of (R)-albuterol and (S)albuterol. Only the (R)-isomer, levalbuterol (LEV), is therapeutically active. Lower doses of LEV, devoid of (S)-albuterol, have demonstrated efficacy comparable to that of higher doses of the (R)-isomer administered as a component of RAC.

OBJECTIVE: The purpose of this study was to determine whether LEV results in improved safety and efficacy in children.

METHODS: Asthmatic children aged 4 to 11 years (n =338; FEV(1), 40% to 85 % of predicted) participated in this multicenter, randomized, double-blinded study and received 21 days of 3-times-a-day treatment with nebulized LEV (0.31 or 0.63 mg), RAC (1.25 or 2.5 mg), or placebo. The primary endpoint was FEV(1) (peak percent change). Adverse events, clinical laboratory test results, vital signs, and electrocardiograms were evaluated for safety.

RESULTS: All active treatments significantly improved the primary endpoint in comparison with placebo (P <.001). Significant differences in FEV(1) were noted immediately after nebulization (median change, 2.0%, 19.0%, 18.1 %, 12.4%, and 15.6% for placebo, LEV 0.31 and 0.63, RAC 1.25 and 2.5 mg, respectively; P <.05 vs placebo; P <.05 for LEV 0.31 and 0.63 vs RAC 1.25 mg). LEV 0.31 mg was the only treatment not different from placebo for changes in ventricular heart rate, QT(c) interval, and glucose (P >.05). All active treatments decreased serum potassium (range, -0.3 to -0.6; P <.002 vs placebo), and RAC 2.5 mg caused the greatest change (P <.005 vs other actives). In a patient subset with severe asthma, a dose-response relationship was observed for levalbuterol, indicating that higher doses were more effective.

CONCLUSION: LEV was clinically comparable to 4- to 8-fold higher doses of RAC, and it demonstrated a more favorable safety profile. LEV 0.31 mg should be used as the starting dose in 4-11 year old children with mild to moderate persistent asthma. Patients with severe disease might benefit from higher doses.

J Allergy Clin Immunol. 1998 Dec;102(6 Pt 1):943-52.

Improved bronchodilation with levalbuterol compared with racemic albuterol in patients with asthma.

Nelson HS, Bensch G, Pleskow WW, DiSantostefano R, DeGraw S, Reasner DS, Rollins TE, Rubin PD.

National Jewish Medical and Research Center, Denver, CO, USA.

BACKGROUND: Racemic albuterol is an equal mixture of (R)-albuterol (levalbuterol), which is responsible for the bronchodilator effect, and (S)-albuterol, which provides no benefit and may be detrimental.

OBJECTIVE: We sought to compare 2 doses of a single enantiomer, levalbuterol (0.63 mg and 1.25 mg), and equivalent amounts of levalbuterol administered as racemic albuterol with placebo in patients with moderate-to-severe asthma.

METHODS: This was a randomized, double-blind, parallel-group trial. Three hundred sixty-two patients 12 years of age or older were treated with study drug administered by means of nebulization 3 times daily for 28 days. The primary endpoint was peak change in FEV1 after 4 weeks.

RESULTS: The change in peak FEV1 response to the first dose in the combined levalbuterol group was significantly greater compared with the combined racemic albuterol group (0.92 and 0.82 L, respectively; $P = .03$), with similar but nonsignificant results after 4 weeks (0.84 and 0.74 L, respectively). Improvement in FEV1 was similar for levalbuterol 0.63 mg and racemic albuterol 2.5 mg and greatest for levalbuterol 1.25 mg. Racemic albuterol 1.25 mg demonstrated the weakest bronchodilator effect, particularly after chronic dosing. The greatest increase in FEV1 was seen after levalbuterol 1.25 mg, especially in subjects with severe asthma. All active treatments were well tolerated, and beta-adrenergic side effects after administration of levalbuterol 0.63 mg were reduced relative to levalbuterol 1.25 mg or racemic albuterol 2.5 mg. At week 4, the predose FEV1 value was greatest in patients who received levalbuterol or placebo when compared with those who received racemic albuterol. The difference was more evident and was statistically significant in patients who were not receiving inhaled corticosteroids.

CONCLUSION: Levalbuterol appears to provide a better therapeutic index than the standard dose of racemic albuterol. These results support the concept that (S)-albuterol may have detrimental effects on pulmonary function.

Am J Emerg Med. 2004 Jan; 22(1):29-36.

Levalbuterol compared with racemic albuterol in the treatment of acute asthma: results of a pilot study.

Nowak RM, Emerman CL, Schaefer K, Disalltostefano RL, Vaickus L, Roach JM.

Henry Ford Health System, Detroit, Michigan 48202, USA. mowak1@hfhs.org

This was a prospective, open-label, nonrandomized pilot study to evaluate efficacy and tolerability of levalbuterol (LEV) in acute asthma. Asthmatics (forced expiratory volume in 1 second [FEV1], 20-55%predicted) were sequentially enrolled into cohorts of 12 to 14 and received 0.63, 1.25, 2.5, 3.75, or 5.0 mg LEV or 2.5 or 5.0 mg racemic albuterol (RAC) every 20 minutes x 3. After the first dose, FEV1 changes were 56% (0.6 L) for 1.25 mg LEV and 6% (0.07 L) and 14% (0.21 L) for 2.5 and 5 mg RAC respectively. After three doses, FEV1 changes were 74% (0.9 L), 39% (0.5 L), and 37% (0.6 L) for 1.25 mg, LEV 2.5 mg, RAC and 0.63 mg LEV respectively. LEV doses greater than 1.25 mg did not further improve bronchodilation. Baseline plasma (S)-albuterol levels were negatively correlated with baseline FEV1 ($R = -0.3$, $P = .004$) and percent change in FEV1 ($R = -0.3$, $P = .006$). LEV at a dose of 1.25 mg produced effective bronchodilation that was greater than both RAC doses. The negative correlation between (S)-albuterol levels and FEV1 could suggest a deleterious effect of (S)-albuterol. Larger comparative studies are warranted.

ATS Meeting Detail (continued)
Orlando, Florida
May 21-26.2004

Attachment 6
(Copied &pasted from ATS website)

[B36] [Poster: G5] Levalbuterol (LEV) vs Racemic Albuterol (RAC) In Acute Severe Asthma: A Prospective Trial

R. Nowak, C. Emerman, R. Claus, K. Schaefer, W. McVicar, J.P. Hanrahan, R.A. Baumgartner
Henry Ford Hospital, Detroit, MI; Case Western Reserve University, Cleveland, OH; Sepracor
Inc, Marlborough, MA

Rationale: Inhaled short-acting β_2 -agonists are a cornerstone therapy of asthma exacerbations. This trial compared the efficacy of nebulized LEV vs RAC in severe asthma.

Methods: Among 627 patients in this randomized, double-blind, multicenter trial of adults with acute asthma (mean FEV₁ predicted 37.9 ± 10.3 on presentation), 315 received LEV 1.25 mg and 312 received RAC 2.5 mg nebulized q 20 min in the 1st hr, and q 40 min thereafter for up to 3 hrs. Clinical and FEV₁ assessments were performed after each dose, and the Time to Meet Discharge Criteria (TDC) was assessed. TDC was based either on objective criteria (FEV₁, 70% predicted or 2.1 L plus no wheeze and good air movement) or physician-assessed clinical stability.

Results: Asthma severity was comparable in both groups based on presenting FEV₁ level, rescue MDI use, prior corticosteroid use, and ED visits and hospital admissions in the past year. FEV₁ improvement was greater in the LEV-treated patients, both after the first dose (LEV 0.504 vs RAC 0.433 L; p=0.021) and averaged over the 3 hr acute treatment period (LEV 0.654 vs RAC 0.580 L; p=0.038). Among those discharged median TDC was similar LEV (76 min) and RAC (79 min). However, > 65% of patients were discharged based on physician-assessed improvement without attaining the pre-specified FEV₁ level (70% predicted). Time to Event analysis incorporating the discharge criteria of good air movement, resolution of wheezing, and reaching FEV₁ of 64% predicted (the median FEV₁ observed at discharge for all patients) demonstrated faster improvement in LEV-treated patients (p=0.046). Similar Time to Event analyses based on attaining FEV₁ discharge values between 40%-75% predicted consistently favored LEV.

Conclusion: In acute asthma, levalbuterol accelerates improvement in FEV₁ when compared with RAC.

Monday, May 24.2004 8:15 AM

[] Thematic Poster Session (Abstract Page: A310) Session: 8:15 am - 4:15 pm, ASTHMA THERAPY: BRONCHODILATORS**

**American College of Allergy, Asthma & Immunology
November 16-21, 2001
Orlando, FL**

Physicians and patients prefer levalbuterol to racemic albuterol. J.A. Ohar, St. Louis, MO, USA; D.R. Grogan and K. Schaefer, Marlborough, MA, USA.

Levalbuterol (LEV), the single isomer of racemic albuterol (RAC), is approved for the treatment and prevention of bronchospasm. To assess the preference for LEV treatment, patients with asthma or COPD (with reversible component) on nebulized RAC were enrolled into a 12 week open label, noncomparative, multicenter study of the effects of LEV 0.63 or 1.25 mg as prescribed by the enrolling physician. The patients' response and side effects to current therapy were assessed at baseline Visit 1 (RAC) and at end of study Visit 2 (LEV). A total of 639 patients were enrolled (363 asthma, 276 COPD), with an average age of 57 years (48 years asthma, 69 years COPD). Most (68%) had disease duration > 5 years, over 80% of asthmatics had moderate or severe persistent asthma, and 67% of COPD patients had peak flow rate < 50% predicted. Two-thirds of the patients were treated with 0.63 mg LEV, with over 60% of both dosage groups prescribed at least TID dosing. Of those patients completing both Visits, 67% preferred LEV therapy to RAC. Over 50% reported that they were very satisfied with relief of symptoms following LEV treatment compared to 27% on RAC (overall $p < 0.001$). At the beginning of the study, 30% of patients reported their disease as severe, compared to 16% after 12 weeks of LEV treatment (overall $p < 0.001$). At Visit 1, 75% of patients reported exacerbations within the previous 12 weeks, compared to 25% during 12 weeks of treatment with LEV. Sixty-two percent experienced fewer side effects on LEV compared with RAC. Approximately 70% of investigators preferred LEV treatment and would continue to prescribe LEV for the patient. Results were similar when data was stratified by dose and disease. Overall, the treatment was well tolerated, with 27% of patients reporting an adverse event, with asthma exacerbation being the most common (15% and 13% in 0.63 mg and 1.25 mg dose group respectively). In conclusion, patients with reversible bronchospasm, including moderate to severe asthma and elderly patients with COPD, as well as prescribing physicians, prefer nebulized LEV over RAC, with improvement in disease symptoms and decreases in side effects.

Ohar J, Grogan D, Schaefer K. Physicians and patients prefer levalbuterol to racemic albuterol [abstract]. *Ann Allergy Asthma Immunol* 2002; 88:132

COMPARISON IN RATES OF BREAKTHROUGH TREATMENTS DURING A CONVERSION FROM RACEMIC ALBUTEROL TO LEVALBUTEROL

Robert S Pikarsky, BSRT *. Russell A. Acevedo. MD. FCCP. Charles Roman. RRT and Tracey Farrell. RRT. Respiratory Care, Crouse Hospital, Syracuse, New York. Chest 122: 146S, 2002

Purpose: In order to meet our patient care demands, Crouse Hospital approved an automatic conversion from Racemic Albuterol to Levalbuterol. This study compares the breakthrough rates of Racemic Albuterol and Levalbuterol, with and without Ipratropium.

Methods: Racemic Albuterol (Alb) 2.5 mg Q4h was converted to either Levalbuterol (Lev) 0.63 mg Q6h or Levalbuterol 1.25 mg Q8h. If ordered, Ipratropium (Ipra) 0.5 mg was administered at the same frequency as the Levalbuterol. Patients with acute coronary syndromes, need for cardiac monitoring, or requiring more frequent aerosol administration received the lower Levalbuterol dose Q6h. A majority of aerosol therapy was provided with the use of the AeroEclipse Breath Actuated Nebulizer (BAN). All aerosol treatments, including breakthrough treatments, delivered between July 1, 2001 and February 28, 2002 were recorded.

Results: Tx/Pt/day represents the number of treatments delivered per patient per day. $\text{Rate}/100 \text{ Pt}/\text{days} = (\text{Breakthrough}) / (\text{Total Tx} / \text{Tx}/\text{Pt}/\text{day}) \times 100$. Rate/100 Pt/days corrects for the differences in daily administration frequency, and may better reflect the daily impact of the breakthrough rate. The breakthrough rate of the combined Albuterol group was significantly greater than both Levalbuterol groups (5.29 vs. 2.29, 5.29 vs. 2.43, $p < .001$)*. The breakthrough rate with Albuterol was significantly reduced with the addition of Ipratropium ($p < .001$)**.

Ipratropium did not significantly change the breakthrough rate when added to Levalbuterol groups.

Medication	Total Tx	Breakthrough	Rate/1000	Tx/Pt/day	Rate/100 Pt/day	
Alb Q4h	3832	47	12.27	6	7.36**	5.29*
Alb/Ipra Q4h	3767	20	5.31	6	3.19**	*
Lev 0.63 Q6h	3592	24	6.68	4	2.67	2.29*
Lev 0.63 mg/Ipra Q6h	1821	7	3.84	4	1.54	*
Lev 1.25mg Q8h	1791	17	9.49	3	2.85	2.43*
Lev 1.25mg/Ipra Q8h	678	3	4.42	3	1.33	*

Conclusions: The conversion from Racemic Albuterol to Levalbuterol allowed for a decreased frequency of daily medication administrations and a significant decrease in breakthrough requirements. Ipratropium showed a significant benefit in breakthrough reduction for the Racemic Albuterol group.

Clinical Implications: The efficiencies gained by decreasing the daily frequency of aerosol administration can have a significant impact on resource utilization. The conversion to Levalbuterol allows for decreased respiratory therapy time or the reallocating of workforce needs while maintaining, or improving, quality of aerosol administration, as evidenced by the decrease in breakthrough requirements.

Allergy Asthma Proc. 2004 Nov-Dec;25 (6):429-36.

Pairwise comparison of levalbuterol versus racemic albuterol in the treatment of moderate-to-severe asthma.

Pleskow WW, Nelson HS, Schaefer K, Claus R, Roach JM.

Radiant Research, Encinitas, California, USA.

The object of this study is a post hoc pairwise comparison of levalbuterol versus racemic albuterol for asthma in a multicenter, double-blind, randomized, placebo-controlled clinical trial. The participants are patients ≥ 12 years of age ($n = 362$) with FEV₁ 45-70 % of predicted. The patients received nebulized levalbuterol (0.63 or 1.25 mg), racemic albuterol (1.25 or 2.5 mg), or placebo t.i.d. for 4 weeks. The primary endpoints, published in Nelson HS, Bensch G, Pleskow WW, et al. Improved bronchodilation with levalbuterol compared with racemic albuterol in patients with asthma. *J Allergy Clin Immunol* 102:943-952, 1998, included comparisons of active treatments with placebo and of the combined levalbuterol with the combined racemic albuterol groups for pulmonary function and rescue medication use. After the first dose, levalbuterol 1.25 mg produced a significantly greater increase in the mean peak change in FEV₁ compared with both doses of racemic albuterol ($p < 0.03$) in all patients and in those with more severe asthma. Levalbuterol 1.25 mg also produced a significantly greater ($p < 0.05$) mean area under the curve (AUC) of the FEV₁ versus time plot (AUC FEV₁) compared with all other treatments after the first dose in all patients and in the subset with more severe disease, illustrating better overall improvement in FEV₁. Active treatment groups demonstrated significant improvements compared with the placebo group ($p < 0.05$), except for AUC FEV₁ in the racemic albuterol 1.25-mg group at week 4. Levalbuterol in the absence of the (S)-isomer provided greater bronchodilation than the same quantity of (R)-albuterol delivered as the racemate. These data suggest that (S)-albuterol may compromise the efficacy of (R)-albuterol.

**Presented at the
ACAAI Annual Meeting
Seattle, WA
November 3-8, 2000**

Patients and Physicians Prefer Levalbuterol over Racemic Albuterol: A Comparison Preference Study. JM Portnoy, MD*, Kansas City, MO, MJ Noonan, MD, Portland, OR, BE Chipps, Sacramento, CA.

Levalbuterol Hcl (Lev), a new 3rd generation beta-agonist, consists of the single isomer (R)-albuterol. Prior studies indicated that 0.63 mg of Lev was clinically comparable to 2.5 mg of racemic albuterol (Rac, a 50:50 mixture of (R)- and (S)-albuterol), with 50% fewer beta-mediated side effects (SE). A large patient survey reported that up to 79 % of patients are concerned about SE and would prefer an alternative (White, 1999). To determine if physicians prefer Lev and to evaluate SE, patients were switched from Rac and evaluated in an open-label study. Patients with stable asthma (n=331 enrolled, 276 complete; mean age=28.3 yrs) were switched from Rac to Lev 0.63 mg via nebulization up to TID for 6-12 weeks. At baseline, 99 % of patients were concerned about SE from asthma therapy and up to 81% reported SE. Over half of patients > 11 yrs reported jitteriness, racing heart, tremors, and nervousness following Rac, while caregivers of children 5-11 yrs (n=90) reported hyperactivity and difficulty going to sleep (Table). Following Lev 0.63 mg, SE were absent or diminished in 84-91% of the patients reporting them at Visit 1, and 76-89% of all patients reported improved SE (Table). Eighty-nine percent of physicians preferred Lev to Rac and 87 % indicated they would continue Lev. Lev 0.63 mg resulted in substantial decreases in beta-mediated SE and was preferred by 89% of physicians. Lev 0.63 mg offers a reduced side-effect profile at a clinically equivalent dose of Rac, indicating an improved therapeutic index.

	SE at Visit 1 N (%)	SE at Visit 2 N (%)
Age > 11 years	N=186	
Jitteriness	133 (72%)	23 (12%)
Racing Heart	129 (70%)	21 (11%)
Tremors	118 (64%)	24 (13%)
Nervousness	101 (54%)	25 (13%)
Age 5-11	N=90	
Hyperactivity	73 (81%)	18 (21%)
Difficulty going to sleep	47 (52%)	21 (24%)

* Assessed by caregiver

Am J Emerg Med. 2005 Nov;23 (7):842-7.

Comparison of racemic albuterol and levalbuterol in the treatment of acute asthma in the ED.

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BACKGROUND: Acute asthma is often treated with racemic albuterol, a 1:1 mixture of (R)-albuterol and (S)-albuterol. Levalbuterol is the single-isomer agent comprised (R) - albuterol, an active bronchodilator, without any effects of (S)-albuterol.

OBJECTIVE: To compare emergency department (ED) admission rates of patients presenting with acute asthma who were treated with either racemic albuterol or levalbuterol.

SETTING: Suburban community teaching hospital.

DESIGN: Retrospective observational case review.

METHODS: Emergency department patients presenting with acute asthma at 2 different sites were reviewed over 9- and 3-month consecutive periods. Outcome measures included ED hospital admission rate, length of stay, arrival acuity, and treatment costs. Patients were excluded if younger than 1 year or if no treatment of acute asthma was rendered.

RESULTS: Of the initial 736 consecutive cases, significantly fewer admissions (4.7% vs 15.1 %, respectively; $P = .0016$) were observed in the levalbuterol vs racemic albuterol group. Of the subsequent 186 consecutive cases, significantly fewer admissions were also observed (13.8% vs 28.9%, respectively; $P = .021$) in the levalbuterol vs racemic albuterol group. Treatment costs were lower with levalbuterol mainly because of a decrease in hospital admissions.

CONCLUSION: Levalbuterol treatment in the ED for patients with acute asthma resulted in higher patient discharge rates and may be a cost-effective alternative to racemic albuterol.

Chest. 2003 Jan; 123 (1):128-35.

Levalbuterol compared to racemic albuterol: efficacy and outcomes in patients hospitalized with COPD or asthma.

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STUDY OBJECTIVES: To compare clinical efficacy, patient outcomes, and medical costs in hospitalized patients treated with levalbuterol to those treated with racemic albuterol.

DESIGN: Retrospective chart review.

SETTING: A 180-bed community hospital.

PATIENTS: Patients admitted to Halifax Regional Hospital with a diagnosis code for COPD or asthma from July 1 to December 31, 1998, and from July 1 to December 31, 1999, were eligible. In 1998, 125 patients were treated with nebulized racemic albuterol (2.5 mg q4h). In 1999, 109 patients were treated with levalbuterol (1.25 mg q8h).

Measurements and results: Clinical efficacy was evaluated by the number of nebulizer treatments, improvement in symptoms and objective clinical findings, the length of hospital stay, and hospital discharge disposition. Medication and total hospital costs were calculated based on Red Book listings and Medicare reimbursement rates. Levalbuterol-treated patients required significantly fewer treatments with beta-agonists (mean [± SD] number of treatments, 19.0 ± 12.7 vs 30.8 ± 24.0; $P < 0.001$) and ipratropium bromide (mean number of treatments, 9.4 ± 11.5 vs 23.2 ± 25.1; $P < 0.001$) than did racemic albuterol-treated patients. The mean length of hospital stay in the levalbuterol group was almost 1 day less than that in the racemic albuterol group (4.7 ± 2.9 vs 5.6 ± 4.2 days, respectively; $p < 0.058$). Significantly more patients were readmitted to the hospital within 30 days in the racemic albuterol group compared with the levalbuterol group (16.4% vs 5.7%, respectively; $p = 0.01$). The mean total cost of nebulizer therapy was significantly greater for patients receiving racemic albuterol than for those receiving for levalbuterol (\$112 ± 101 vs \$61 ± 43, respectively; $p < 0.001$). The mean total hospital costs per patient were less for levalbuterol compared with racemic albuterol (\$2756 ± 2079 vs \$3225 ± 2714, respectively; $p = 0.11$). Regression analysis controlling for diagnosis, baseline FEV₁, and ipratropium use indicated that levalbuterol was associated with a length-of-stay savings of 0.91 days ($p = 0.015$), a totalcost savings of \$556 ($p = 0.013$), and a decrease in the likelihood of hospital readmission of 67% ($p = 0.056$).

CONCLUSION: Compared with patients treated with racemic albuterol, those treated with levalbuterol required less medication, had shorter lengths of hospital stay, had decreased costs for nebulizer therapy and hospitalization, and appeared to have a more prolonged therapeutic benefit. These findings support using levalbuterol as first-line therapy for hospitalized adults with COPD or asthma.

707 Impact of Decreasing Doses of Racemic Albuterol and Levalbuterol on Efficacy: A Pooled Analysis

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 Marlborough, MA

Doses of β_2 -agonists are routinely decreased in an effort to reduce β_2 -mediated side effects, especially in the young and old. However, the impact of dose-reduction on efficacy has not been thoroughly evaluated. Racemic albuterol (Rac) is a 50:50 mix of (R)-albuterol (Levalbuterol, Lev) and (S)-albuterol. Lev 0.63mg is clinically comparable to Rac 2.5mg with fewer side effects. To determine whether decreasing the dose of Rac or Lev effects efficacy, data from 4 asthma studies were pooled (2 pediatric and 2 adult studies, age 4-80 yrs, n = 1538). Immediately post-treatment with Lev 0.63 or 1.25mg, Rac 1.25 or 2.5 mg, or placebo, serial pulmonary function tests were performed. Lev 1.25 consistently produced changes that were significantly greater than Rac 2.5 (FEV₁ mean % change and % change 15 min post-dose, p<0.02), and significantly greater than Rac 1.25 and Lev 0.63. Lev 0.63 was not significantly different than Rac 2.5 for any FEV₁ parameters or in the % of patients responding 15 min post-dose. However, decreasing the Rac dose to 1.25 significantly decreased efficacy compared to all other active treatments (p<0.001). There were significantly fewer responders in the Rac 1.25 group compared with Lev 0.63 and Rac 2.5, and a trend for more responders was noted in favor of Lev 1.25 compared with Rac 1.25 (p=0.076). The rank order of efficacy was Lev 1.25 > Lev 0.63 Rac 2.5 > Rac 1.25. Decreasing the dose of Lev from 1.25 to 0.63 resulted in efficacy that was significantly less than Lev 1.25, but not significantly different than Rac 2.5. Decreasing the dose of Rac to 1.25 produced a significant reduction in efficacy compared with all other active treatments, and was effective in significantly fewer patients. These data demonstrated that decreasing the dose of Rac resulted in suboptimal therapy.

Pulmonary Functional Parameters

	Placebo (n=361)	Lev 0.63 lev (n=373)	Lev 1.25 (n=292)	Rac 1.25 (n=151)	Rac 2.5 (n=367)
FEV1: Mean % Chg	10.6 (.96)	26.9 (0.95)	32.7 (1.07)	20.4 (1.49)	29.3 (0.96)
FEV1: Peak % Chg	22.6 (1.15)	40.5 (1.13)	46.0 (1.28)	32.2 (1.78)	42.9 (1.14)
FEV1: % Chg Time 15	8.8 (1.07)	32.5 (1.05)	38.4 (1.18)	24.1 (1.64)	33.6 (1.05)
% Responders Time 15	25.8	82.2	85.9	64.9	81.7

LSMeans (SEM) presented; Responder: FEV₁, (change from baseline) >15%; Time 15=15 min post-dose; *0.001 vs placebo; '0.001 vs Lev 0.63; *0.003 vs Lev 1.25; #0.001 vs Rac 1.25; ^0.02 vs Rac 2.5; p=0.036 vs Rac 2.5 and 0.017 vs Lev 0.63; °p=0.017 vs Rac 1.25; §p=0.017 vs Rac 1.25.

Vaickus L, Schaefer K, Claus R. Impact of Decreasing Doses of Racemic Albuterol and Levalbuterol on Efficacy: A Pooled Analysis [abstract]. J Allergy Clin Immunol 2002; 109:S233

DUONEB

Chest. 2001 Jan; 119 (1):85-92.

The impact of combined inhaled bronchodilator therapy in the treatment of COPD.

Benayoun S, Ernst P, Suissa S.

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BACKGROUND: Treatment guidelines recommend concomitant use of ipratropium bromide and inhaled beta₂-agonists as severity of COPD progresses. While the use of these two agents in a single inhaler may enhance patient compliance and result in cost savings, it may, by itself, increase medication use. We assessed whether the introduction of a combined inhaled bronchodilator in the treatment of COPD modifies the use and costs related to prescribed medications.

METHOD: A cohort of subjects ≥ 45 years old initiating treatment with either a combined inhaled bronchodilator (641 subjects) or ipratropium bromide and inhaled beta₂-agonist (411 subjects) between July 1, 1996, and June 30, 1997, was identified using the Saskatchewan Health databases. The primary outcomes were prescribed medication usage and the subsequent related costs during a 1-year follow-up period. Poisson regression analysis was used to estimate rate ratios (RRs) adjusted for drug use and hospitalization during the year prior to cohort entry.

RESULTS: The adjusted RR of inhaled bronchodilator use was elevated for combined inhaled bronchodilator therapy (adjusted RR, 1.16; 95% confidence interval [CI], 1.07 to 1.26). However, the overall costs associated with these inhaled bronchodilators were reduced with combined inhaled bronchodilator therapy (adjusted mean ratio, 0.83; 95% CI, 0.76 to 0.92). The rate of use of other respiratory drugs and antibiotics was similar (adjusted RR, 1.03; 95% CI, 0.93 to 1.16). Applying the rate ratio for cost savings to all new, combined inhaled bronchodilator users led to estimated annual savings in Canadian dollars of 103,468 dollars (95% CI, 48,694 dollars to 146,082 dollars) in this province.

CONCLUSION: The introduction of a simpler bronchodilator dosing regimen did not significantly alter the treatment of COPD and resulted in appreciable cost savings.

Am J Manag Care. 2002 Oct;8 (10) :902-11.

Delivery of ipratropium and albuterol combination therapy for chronic obstructive pulmonary disease: effectiveness of a two-in-one inhaler versus separate inhalers.

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OBJECTIVE: To determine whether a combined formulation consisting of ipratropium and an inhaled beta₂ agonist (2-in-1 therapy) leads to lower respiratory-related healthcare use and charges and improved compliance compared with treatment with separate ipratropium and beta₂-agonist inhalers (separate inhaler therapy).

STUDY DESIGN: Retrospective inception cohort study.

PATIENTS AND METHODS: Healthcare use, charges, and treatment compliance were examined for adults age 38 years or older who initiated ipratropium therapy on or after July 1997, based on health claims data for United Healthcare enrollees from 5 health plans from July 1997 through December 1998. A total of 428 patients received 2-in-1 therapy, and 658 patients received separate inhaler therapy. To adjust for disease severity and other confounders, the following were determined for the preinitiation period: age; sex; use of oral steroids, antibiotics, or albuterol; respiratory-related healthcare use; and respiratory diagnoses. Compliance was defined as not interrupting or discontinuing therapy during the follow-up period.

RESULTS: After adjusting for baseline covariates, 2-in-1 therapy users had a significantly lower risk of emergency department use or hospitalization (relative risk = 0.58, 95% confidence interval [CI] = 0.36, 0.94), lower mean monthly healthcare charges (P = .015), shorter hospital stays (2.05 vs 4.61 days, P = .040), and greater likelihood of compliance (odds ratio = 1.77, 95% CI = 1.46, 2.14).

CONCLUSION: A single inhaler containing both ipratropium and albuterol can increase compliance and decrease respiratory morbidity and charges over and above the effects achieved with separate inhalers for these 2 agents.

Chest. 1997 Dec;112 (6):1514-21.

Routine nebulized ipratropium and albuterol together are better than either alone in COPD. The COMBIVENT Inhalation Solution Study Group.

[No authors listed]

STUDY OBJECTIVE: We compared the long-term safety and efficacy of the combination ipratropium bromide (IB) and albuterol sulfate (ALB) inhalation solution with that of each separate component using three-times-daily administration.

DESIGN: Using a parallel design, we randomized patients to receive 3.0 mg ALB, 0.5 mg IB, or the combination by small-volume nebulizer (SVN) for 85 days. Subjects were allowed to use up to two extra doses of study medication daily for control of symptoms on an as-needed basis. The main efficacy evaluation was the acute pulmonary function response to an aerosol of the maintenance study medication over the course of the investigation. Physician global evaluation, subject quality of life assessments, COPD symptom scores, and twice-daily peak expiratory flow rate (PEFR) were also assessed over the study period.

SETTING: Twenty-five centers participated in the investigation.

PATIENTS: We studied 652 patients with moderate to severe COPD.

MEASUREMENTS AND RESULTS: Over the course of the study, the acute spirometric response and evening PEFR values with the SVN combination of IB plus ALB were statistically significantly better compared to ALB or IE alone. The quality of life scores, physician global evaluations, symptom scores, and morning PEFR scores were unchanged over the duration of the study in all treatment groups. There was no significant difference in adverse events in the three treatment groups.

CONCLUSIONS: In patients with COPD, maintenance SVN therapy with IB and ALB provides better bronchodilation than either therapy alone without increasing side effects.

Proc Am Thorac Soc. 2005;2 (4):272-81; discussion 290-1.

Combination therapy for chronic obstructive pulmonary disease: clinical aspects.

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Anticholinergics and beta-agonists reduce bronchoconstriction through different mechanisms, and there is a long history of combination therapy with short-acting agents in these classes for chronic obstructive pulmonary disease. Such combinations may allow lower doses and thereby improve safety. Oral theophylline has also been combined with short-acting bronchodilators for many years. Most studies, however, show only mild improvements in bronchodilation at the expense of increased adverse effects. Professional society guidelines recommend that as the symptoms of chronic obstructive pulmonary disease progress, the patient should receive regular treatment with one or more long-acting bronchodilators, and an inhaled corticosteroid if the patient has repeated exacerbations. The combination of a short-acting anticholinergic with a long-acting beta-agonist, or the combination of a long-acting anticholinergic with a short- or long-acting beta-agonist, has been shown in most studies to improve lung function versus monotherapy with the individual components. Systematic reviews have concluded that fluticasone and salmeterol, and budesonide and formoterol, are superior to placebo and lead to clinically meaningful improvements in lung function, exacerbation rate, and quality of life. Effects on survival are less clear. Some of the other issues to be resolved are the safety of combination therapy, its pharmacoeconomic impact, and the role of newer agents.

Chest. 1999 Mar; 115(3):635-41.

Pharmacoeconomic evaluation of a combination of ipratropium plus albuterol compared with ipratropium alone and albuterol alone in COPD.

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STUDY OBJECTIVE: To conduct a post hoc pharmacoeconomic evaluation of two double-blind, randomized, prospective, parallel group studies comparing the long-term efficacy and safety of ipratropium combined with albuterol in a single inhalational canister against either bronchodilator agent alone in patients with COPD. Patients: One thousand sixty-seven patients with COPD.

METHODS: The dose of each bronchodilator was two puffs four times a day (42 microg of ipratropium bromide, 240 microg of albuterol sulfate). Pulmonary function testing was performed on days 1, 29, 57, and 85 of treatment. Outcomes, health-care resource consumption, and costs were compared for the three treatment groups over the 85-day study period. A total of 1,067 patients were randomized in the two studies (albuterol alone, n=347; ipratropium alone, n=362; albuterol plus ipratropium, n=358).

RESULTS: Improvement in FEV1 and area under the FEV1 response-time curve from time 0 to 4 h (FEV1AUC0-4) was significantly greater for the combination of albuterol plus ipratropium than either agent alone on all test days. Compared with albuterol, patients receiving ipratropium and ipratropium plus albuterol experienced significantly fewer COPD exacerbations and patient-days of exacerbation. In addition, the increased frequency of exacerbations observed in the albuterol group was associated with a significant increase in the number of patient hospital days and antibiotic and corticosteroid use. As a result, the total cost of treatment over the study period was significantly less for ipratropium (\$156 per patient) and ipratropium plus albuterol (\$197 per patient) than for albuterol (\$269 per patient). Increased cost-effectiveness, defined as total estimated treatment cost per mean change in FEV1AUC0-4, was observed in both treatment arms containing ipratropium.

CONCLUSIONS: The inclusion of ipratropium in a pharmacologic treatment regimen is associated with a lower rate of exacerbations in COPD. The result is lower total treatment costs and improved cost-effectiveness.

Respiration. 1998; 65(5):354-62.

Inhalation by nebulization of albuterol-ipratropium combination (Dey combination) is superior to either agent alone in the treatment of chronic obstructive pulmonary disease. Dey Combination Solution Study Group.

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Combination bronchodilator therapy for chronic obstructive pulmonary disease (COPD) potentially can provide increased benefit over single-agent therapy. The objective of this double-blind, randomized, positive-control trial was to determine the effectiveness of an albuterol-ipratropium solution aerosol combination (Dey combination solution, Dey LP, Napa, Calif., USA) compared with solution aerosols of both component medications administered alone in patients with COPD. The trial consisted of a 6-week, 3-period crossover phase followed by a 6-week parallel phase during which patients self-administered study medications by inhalation from a nebulizer. A total of 863 patients were initially randomized to each of the six possible treatment sequences of the three study medications in the crossover phase and received each study medication in turn for a 2-week period. Patients continued to receive the same treatment administered during the last 2-week period of the crossover phase for an additional 6 weeks in the parallel phase. Assessment of 1-second forced expiratory volume (FEV₁) curves before and after dosing on the last day of each 2-week period indicated that the combination was superior to either single agent in peak effect and area under the curve up to 8 h after dosing (FEV₁-AUC₀₋₈), in both phases of the trial. The use of Dey combination during the crossover phase resulted in 24% more improvement in peak FEV₁ than was seen with albuterol alone ($p < 0.001$), and 37% more than was seen with ipratropium alone ($p < 0.001$). Similarly, when examining FEV₁-AUC₀₋₈, Dey combination resulted in 30% more improvement than was seen with albuterol alone ($p < 0.001$), and 32% more than was seen with ipratropium alone ($p < 0.001$). The combination affords a convenient dosing regimen and incorporates enhanced benefit without compromising the safety profile of either component agent.

Chest. 1999 May; 115(5):1338-45.

Effect of ipratropium bromide treatment on oxygen saturation and sleep quality in COPD.

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STUDY OBJECTIVES: Patients with COPD are at risk of experiencing a deterioration in arterial oxygen saturation (SaO₂) during sleep, which is generally most pronounced during rapid eye movement (REM) sleep. Increased cholinergic tone has been suggested as a contributing factor to this decrease in SaO₂. Therefore, we investigated whether 4-week treatment with ipratropium bromide inhalation solution 0.02% (qid) could improve sleep characteristics in COPD.

DESIGN: Randomized, placebo-controlled, double-blind, two-arm parallel study of 4 weeks of treatment with ipratropium bromide solution or placebo.

SETTING: Multicenter investigation.

PATIENTS: Thirty-six patients with moderate-to-severe COPD (FEV₁ <65% of predicted).

MEASUREMENTS AND RESULTS: Evaluation included polysomnographic, pulmonary function, and subjective quality of sleep (visual analog scale [VAS]) assessments. It was found that 4 week of treatment with ipratropium bromide solution in patients with COPD led to the following: (1) a significant (p = 0.05) improvement in mean nocturnal SaO₂ with the more severe the nocturnal desaturation, the greater the improvement in SaO₂; (2) significant (p = 0.03) improvement in perceived sleep quality (VAS: 5.5 +/- 0.5 after placebo; 7.2 +/- 0.5 after ipratropium); (3) a significant (p = 0.05) increase in REM sleep time (48.6 +/- 6.3 min after placebo; 66.5 +/- 6.4 min after ipratropium) with no effect on other sleep stages or total sleep time; and (4) a significant (p = 0.01) increase in pre-sleep PVC and flow rate at 50% of the vital capacity.

CONCLUSIONS: These findings demonstrate that ipratropium bromide therapy can improve sleep SaO₂ as well as sleep quality in patients with moderate-to-severe COPD.

Respir Care. 2005 Oct; 50(10):1346-56; discussion 1357-9.

Determinants of patient adherence to an aerosol regimen.

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Patient adherence with prescribed inhaled therapy is related to morbidity and mortality. The terms "compliance" and "adherence" are used in the literature to describe agreement between prescribed medication and patient practice, with "adherence" implying active patient participation. Patient adherence with inhaled medication can be perfect, good, adequate, poor, or nonexistent, although criteria for such levels are not standardized and may vary from one study to another. Generally, nonadherence can be classified into unintentional (not understood) or intentional (understood but not followed). Failing to understand correct use of an inhaler exemplifies unintentional nonadherence, while refusing to take medication for fear of adverse effects constitutes intentional nonadherence. There are various measures of adherence, including biochemical monitoring of subjects, electronic or mechanical device monitors, direct observation of patients, medical/pharmacy records, counting remaining doses, clinician judgment, and patient self-report or diaries. The methods cited are in order of more to less objective, although even electronic monitoring can be prone to patient deception. Adherence is notoriously higher when determined by patient self-report, compared to electronic monitors. A general lack of adherence with inhaled medications has been documented in studies, and adherence declines over time, even with return clinic visits. Lack of correct aerosol-device use is a particular type of nonadherence, and clinician knowledge of correct use has been shown to be imperfect. Other factors related to patient adherence include the complexity of the inhalation regimen (dosing frequency, number of drugs), route of administration (oral vs inhaled), type of inhaled agent (corticosteroid adherence is worse than with short-acting beta2 agonists), patient awareness of monitoring, as well as a variety of patient beliefs and sociocultural and psychological factors. Good communication skills among clinicians and patient education about inhaled medications are central to improving adherence.

PHARMACOECONOMIC AND COMPLIANCE EVALUATION OF DUONEB VERSUS DUAL SINGLE AGENTS (IPRATROPIUM BROMIDE AND ALBUTEROL) IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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PURPOSE: To compare DuoNeb (DN) versus dual single agents (dual single agents (DSAs: nebulized ipratropium bromide and albuterol) on health care resources and compliance patients with chronic obstructive pulmonary disease (COPD).

METHODS: This retrospective evaluation compared DN and OSA managed care claims for COPD patients (age 40 years, 15 months of plan eligibility) over 12 consecutive months. Per-member-per-month (PMPM) claims (total, medical, inpatient, pharmacy, and emergency department [ED] expenditures) for 12 months were compared on an overall and a "GOLD" subgroup basis, and compliance involved an evaluation of the frequency of interruptions and discontinuations. Statistics included student's *t*, χ^2 , and Wilcoxon signed ranked sum tests.

RESULTS: 1,531 subjects were analyzed: 468 DN and 1,063 DSA. PMPM comparisons included: total (DN \$1,840, DSA \$2,046.73; $P=0.22$); medical (DN \$549.59, DSA \$570.70; $P=0.65$); inpatient (DN \$874.97, DSA \$1,105.80; $P=0.10$); pharmacy (\$415.80 DN, \$370.22 DSA; $P=0.07$); and ED (DN \$36.67, DSA \$52.84; $P=0.03$). Frequency of ED visits were 0.93 for DN and 1.33 for DSA ($P<0001$). DN had fewer claims for stage IV medical ($P=0.05$) and doctor visits ($P=0.006$), ED events for stage II ($P=0.0001$) and IV ($P=0.0001$), and costs/ED event ($P=0.04$). DN versus DSA had fewer therapy interruptions, 0.78 versus 0.85, respectively ($P=0.0003$).

CONCLUSIONS: DN was associated with a significant impact upon ED resources and patient compliance, and lower absolute total, medical, and inpatient expenditures, offsetting higher pharmacy claims (NS) in patients with COPD. Although drug expenditures were found to be higher with DN than OSA, nondrug costs were higher with claims associated with the generic components.

FORMOTEROL

Ann Allergy Asthma Immunol. 2001 Jan; 86 (1):19-27.

A randomized, 12-week, double-blind, placebo-controlled study comparing formoterol dry powder inhaler with albuterol metered-dose inhaler.

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BACKGROUND: Formoterol is a beta2-adrenergic agent which, when inhaled, produces rapid and long-lasting bronchodilatation.

OBJECTIVE: The aim of this study was to compare the efficacy, safety, and tolerability of formoterol powder for inhalation delivered via the Aerolizer device with placebo and with albuterol delivered via metered-dose inhaler in patients with mild to moderate persistent asthma. **METHODS:** In a multicenter, double-blind, parallel-group study, 541 patients were randomized at 26 trial sites to receive either formoterol, 12 microg twice daily; formoterol, 24 microg twice daily; albuterol, 180 microg four times daily; or a placebo for 12 weeks. The effects of each treatment on lung function, asthma symptoms, and frequency of rescue albuterol use were evaluated. Adverse effects and clinical laboratory parameters were also evaluated.

RESULTS: The bronchodilatory effects of formoterol were rapid in onset and persisted for 12 hours. Both formoterol doses were more effective than placebo and albuterol for objective measures of lung function. Morning and evening peak expiratory flow rates were more improved with formoterol, and formoterol provided significantly greater improvements in asthma symptom scores compared with both albuterol and placebo. Overall, patients taking formoterol used significantly less rescue medication than did those taking albuterol or placebo. Nocturnal awakenings occurred less often with formoterol than with placebo or albuterol. The therapeutic effects of formoterol were maintained over the entire 12 weeks of treatment. Adverse events were similar for all treatment groups, and clinical laboratory data were unremarkable.

CONCLUSIONS: Rapid-onset, long-acting formoterol, administered via the Aerolizer inhaler, is an effective and safe treatment for patients with mild to moderate persistent asthma.

Respir Med. 2003 Sep; 97 (9):1067-74.

Formoterol (OXIS) Turbuhaler as a rescue therapy compared with salbutamol pMDI plus spacer in patients with acute severe asthma.

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Formoterol has a similar onset of effect to salbutamol but a prolonged duration of action. However, the relative efficacy of the two drugs in acute severe asthma is not known. This double-blind, double-dummy study compared the safety and efficacy of the maximum recommended daily dose of formoterol and a predicted equivalent dose of salbutamol in 88 patients presenting to the emergency department with acute severe asthma. Patients were randomized to formoterol 54 microg via Turbuhaler or salbutamol 2400 microg via pressurized metered dose inhaler (pMDI) plus spacer in three equal doses over 1 h. Following the full dose, mean FEV1 at 75 min increased by 37% for formoterol and 28% for salbutamol (P =0.18). The maximum increase in FEV1 over 4 h was significantly greater with formoterol compared with salbutamol (51 % vs. 36%, respectively P <0.05) and formoterol was as effective as salbutamol at improving symptoms and wellbeing. Both treatments were well tolerated. Formoterol caused a greater decrease in serum potassium (difference -0.2 mmol/l). In severe acute asthma, bronchodilator therapy with high-dose (54 microg) formoterol Turbuhaler provided equally rapid improvements in lung function of greater magnitude over 4 h than high-dose (2400 microg) salbutamol pMDI plus spacer.

Clin Ther. 2003 Jul; 25 (7):2022-36.

Formoterol 12 microg BID administered via single-dose dry powder inhaler in adults with asthma suboptimally controlled with salmeterol or on-demand salbutamol: a multicenter, randomized, open-label, parallel-group study.

Brambilla C, Le Gros V, Bourdeix I; Efficacy of Foradil in Asthma (EFORA) French Study Group.

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BACKGROUND: Although salmeterol and formoterol are both long-acting beta(2) adrenergic receptor agonist bronchodilators, there are distinct differences between them that could translate into differences in clinical response in some patients.

OBJECTIVE: The goal of this study was to examine the efficacy of formoterol in patients with moderate to severe persistent asthma that was suboptimally controlled with an inhaled corticosteroid (ICS) combined with on-demand salbutamol (albuterol in the United States) with or without salmeterol.

METHODS: This multicenter, 4-week, randomized, open-label, parallel-group study included adult patients (age ≥ 18 years) with suboptimally controlled asthma (mean salbutamol use, ≥ 2 puffs/d via pressurized metered-dose inhaler [100 microg/puff]). Patients were randomized in a 2:1 ratio to receive formoterol 12 microg BID via single-dose dry powder inhaler plus on-demand salbutamol or to continue their existing treatment with either on-demand salbutamol alone or salmeterol 50 microg BID via multidose dry powder inhaler plus on-demand salbutamol. ICS regimens were unchanged during the trial. The primary efficacy variable was evening predose peak expiratory flow (PEF). Secondary variables included further measures of asthma symptom control.

RESULTS: A total of 6239 adult patients entered the study; data from 6155 patients were available for analysis. Patients who were switched from salmeterol to formoterol reported a significant increase in mean (SD) evening predose PEF compared with patients who continued their existing treatment (402.9 [112.1] vs 385.5 [107.5] L/min, respectively; $P < 0.001$). Similarly, patients who were switched from on-demand salbutamol alone to formoterol plus on-demand salbutamol reported a significant increase in mean evening predose PEF compared with those who continued treatment with on-demand salbutamol alone (409.3 [105.6] vs 385.0 [105.3] L/min, respectively; $P < 0.001$). The results for the secondary efficacy measures mirrored the significant improvements seen in patients switched to formoterol compared with those who continued to receive on-demand salbutamol alone or salmeterol plus on demand salbutamol.

CONCLUSION: In this study, formoterol significantly improved lung function and control of asthma symptoms and decreased use of rescue medication in patients whose asthma had been suboptimally controlled with an ICS in combination with on-demand salbutamol with or without salmeterol.

Clin Ther. 2004 Oct; 26 (10):1587-98.

Efficacy, tolerability, and effect on asthma-related quality of life of formoterol bid via multidose dry powder inhaler and albuterol QID via metered dose inhaler in patients with persistent asthma: a multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group study.

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BACKGROUND: Inhaled beta(2)-agonists are widely used in asthma treatment. The design limitations of pressurized metered dose inhalers (PMDIs) have prompted the development of dry powder inhalers (DPIs) for the delivery of asthma medications.

OBJECTIVE: The goal of this study was to evaluate the efficacy, tolerability, and effect on asthma-related quality of life (QOL) of a long-acting beta(2)-adrenoreceptor agonist, formoterol, delivered via multidose DPI, compared with albuterol delivered via pMDI or placebo in adolescents and adults with persistent asthma.

METHODS: This multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group study was conducted in outpatient clinics at 18 US centers. Adolescents and adults with persistent asthma received formoterol 10 µg BID via multidose DPI, albuterol 180 microg QID via pMDI, or placebo for 12 weeks. The primary efficacy variable was the 12-hour AUC of forced expiratory volume in 1 second (FEV₁) after 12 weeks treatment. Secondary efficacy variables included asthma-related QOL, asthma symptom scores, rescue medication use, and other pulmonary function measures.

RESULTS: A total of 239 patients (147 females, 92 males; age range, 13-85 years) with persistent asthma were enrolled (formoterol, n =80; albuterol, n =79; placebo, n =80). Formoterol delivered via the multidose DPI resulted in clinically relevant and statistically significant increases in 12-hour AUC of FEV₁ after 12 weeks of treatment compared with albuterol pMDI and placebo (P <0.019 and P <0.001, respectively). Asthma-related QOL (total score) was significantly improved with formoterol treatment compared with placebo (P <0.015). Nocturnal asthma symptom scores significantly improved with formoterol compared with albuterol and placebo (P <0.001 and P <0.003, respectively) and rescue medication use was significantly less with formoterol compared with albuterol and placebo (P <0.004 and P <0.002, respectively). Treatment with formoterol was well tolerated.

CONCLUSIONS: In this study of adolescents and adults with persistent asthma, 12 weeks of treatment with formoterol 10 microg BID delivered via a multidose DPI provided significantly greater 24-hour bronchodilation compared with albuterol and placebo and resulted in significant improvements in asthma-related QOL compared with placebo. Formoterol was well tolerated in these patients.

Am J Respir Crit Care Med. 2001 Sep 1; 164 (5):778-84.

Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease.

Dahl R, Greefhorst LA, Nowak D, Nonikov V, Byrne AM, Thomson MH, Till D, Della Cioppa G; Formoterol in Chronic Obstructive Pulmonary Disease I Study Group.

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We compared the effectiveness of inhaled formoterol with that of ipratropium in the treatment of chronic obstructive pulmonary disease (COPD). After a 2-wk run-in period, 780 patients with COPD were randomized to receive for 12 wk formoterol dry powder 12 or 24 microg twice daily, ipratropium bromide 40 microg four times daily, or placebo in a multicenter, double-blind, parallel-group study. The primary efficacy variable was the area under the curve for forced expiratory volume in 1 s (FEV(1)) measured over 12 h after 12 wk of treatment. Secondary variables included diary symptoms and quality of life. Both doses of formoterol and ipratropium significantly increased the area under the curve for FEV(1) in comparison with placebo (all $P < 0.001$). Both doses of formoterol were also significantly superior to ipratropium (all $p < 0.025$). Compared with placebo, both doses of formoterol significantly improved symptoms (all $p < 0.007$) and quality of life ($p < 0.01$ for total scores) whereas ipratropium did not show significant effects (all $p \geq 0.3$). All study treatments exhibited a similar safety profile. We conclude that formoterol is more effective than ipratropium bromide in the treatment of COPD, as the efficacy of ipratropium on airflow obstruction does not translate into a clinical benefit that patients can perceive.

Chest. 2001 May; 119 (5):1347-56.

In patients with COPD, treatment with a combination of formoterol and ipratropium is more effective than a combination of salbutamol and ipratropium : a 3-week, randomized, double-blind, within-patient, multicenter study.

D'Urzo AD, De Salvo Me, Ramirez-Rivera A, Almeida J, Sichletidis L, Rapatz G, Kottakis J; FOR-INT-03 Study Group.

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STUDY OBJECTIVES: To compare the efficacy of adding formoterol or salbutamol to regular ipratropium bromide treatment in COPD patients whose conditions were suboptimally controlled with ipratropium bromide alone.

DESIGN: A randomized, double-blind, double-dummy, two-period, crossover clinical trial.

SETTING: Twenty-four clinics and university medical centers in nine countries.

PATIENTS: One hundred seventy-two patients with baseline FEV(1) \leq 65% predicted, with FEV(1) reversibility to salbutamol not exceeding the normal variability of the measurement, and symptomatic despite regular treatment with ipratropium bromide.

INTERVENTIONS: Each patient received two treatments in random order: either inhaled formoterol dry powder, 12 microg bid, in addition to ipratropium bromide, 40 microg qid for 3 weeks, followed by salbutamol, 200 microg qid, in addition to ipratropium, 40 microg qid for 3 weeks, or vice versa.

MEASUREMENTS AND RESULTS: Efficacy end points included morning premedication peak expiratory flow (PEF) during the last week of treatment (primary end point), the area under the curve (AUC) for FEV(1) measured for 6 h after morning dose on the last day of treatment, and symptom scores (from daily diary recordings). Morning PEF and the AUC for FEV(1) were significantly better for formoterol/ipratropium than for salbutamol/ipratropium ($p=0.0003$ and $p<0.0001$, respectively). The formoterol/ipratropium combination also induced a greater improvement in mean total symptom scores ($p=0.0042$). The safety profile of the two treatments was comparable.

CONCLUSIONS: In COPD patients requiring combination bronchodilator treatment, the addition of formoterol to regular ipratropium treatment is more effective than the addition of salbutamol.

Am Rev Respir Dis. 1991 Sep; 144(3 Pt 1):622-5.

A three-month comparison of twice daily inhaled formoterol versus four times daily inhaled albuterol in the management of stable asthma.

Kesten S, Chapman KR, Broder I, Cartier A, Hyland RH, Knight A, Malo JL, Mazza JA, Moote nw, SmallP, et al.

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We compared the efficacy of inhaled formoterol, a long-acting beta 2-agonist, with inhaled albuterol in 145 stable adult asthmatics in a 12-wk multicenter trial. Patients were allocated in randomized double-blind fashion to maintenance therapy with either formoterol 12 micrograms twice a day or albuterol 200 micrograms four times a day in addition to their other asthma medications. Patients were allowed to use "rescue" 100-micrograms albuterol puffs on an as-needed basis. Mean baseline FEV₁ in the morning before bronchodilator was 2.14 +/- 0.76 L and 1.98 +/- 0.71 L for the formoterol and albuterol groups, respectively, these values being used as baseline covariates in subsequent analysis of predrug and postdrug FEV₁. Measured at each clinic visit, morning predrug FEV₁ rose significantly with formoterol treatment and was significantly greater at all visits than in the albuterol group, the greatest difference being in Week 8 (2.40 +/- 0.77 versus 1.92 +/- 0.66 L, P less than 0.001). Morning FEV₁ 30 min postdrug was significantly higher in the formoterol group at Weeks 2 and 8, the trend not reaching statistical significance at other times. Diurnal variation in prebronchodilator peak flow rates was significantly reduced in the formoterol group throughout the trial (17 versus 42 L/min at Week 12, p less than 0.0001). The number of asthma episodes per week was significantly less in the formoterol group during Weeks 4, 8, and 12 as were the number of sleep disruptions during Weeks 2, 4, 6, 8, and 12. Significantly more rescue albuterol was required in the albuterol group by Week 2 and throughout the remainder of the study. (ABSTRACT TRUNCATED AT 250 WORDS)

Int J Clin Pract. 2005 Jan; 59(1):62-8.

Cost-effectiveness of formoterol and salbutamol as asthma reliever medication in Sweden and in Spain.

Lindgren B, Sears MR, Campbell M, Villasante C, Huang S, Lindh A, Petermann W, Svensson K, Berggren F, Pauwels RA; RELIEF study investigators.

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This study aimed to evaluate the cost-effectiveness of formoterol (Oxis) Turbuhaler 4.5 microg and salbutamol 200 microg as reliever medications in Sweden and Spain. The study used data on effectiveness (exacerbations and symptom-free days) and resource utilisation from an open, 6-month, parallel-group, multicentre randomised trial with 18,124 asthma patients in 24 countries. Country-specific unit costs for Sweden and for Spain were used to transform resource utilization data into costs. Total healthcare costs were not significantly different between formoterol and salbutamol dry powder inhalers in Sweden, whereas in Spain, the healthcare costs were 20% higher for formoterol vs. salbutamol pressurised metered dose inhalers. Total healthcare costs increased with disease severity, defined according to the Global Initiative for Asthma guidelines. Compared with salbutamol, formoterol produced statistically significant improvements in effectiveness, less reliever and maintenance medication usage, reduced healthcare resource utilisation, with no increase or a limited increase in healthcare cost.

Am J Respir Crit Care Med. 1999 Jul; 160(1):244-9.

Comparison of the relative efficacy of formoterol and salmeterol in asthmatic patients.

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Studies performed on airway smooth muscle in vitro have indicated that salmeterol is a partial agonist on the beta2-receptor in comparison to formoterol. In the present study we evaluated whether these pharmacological differences between salmeterol and formoterol also are applicable to asthmatic patients. The protective effects by increasing cumulative doses of formoterol (12,60, 120 micrograms) and salmeterol (50,250,500 micrograms) on methacholine-induced bronchoconstriction were evaluated in a double-blind, crossover, placebo-controlled design. Patients were regularly treated with salbutamol 200 micrograms twice daily during the study period, to avoid variability in beta2-adrenoceptor tolerance. S-potassium, heart rate corrected Q-T interval (Q-Tc), and tremor score were followed as measures of systemic effects. Formoterol dose-dependently protected against methacholine responsiveness (4.6 doubling doses after 120 micrograms). Salmeterol, however, showed a flatter dose-response curve, and a significantly weaker maximal protective effect (2.8 doubling doses after 250 micrograms). Formoterol caused a significantly higher tremor score and a larger drop in S-potassium than salmeterol at the highest doses. These data show that salmeterol is a partial agonist on the beta2-receptor in relation to formoterol in human airways in vivo. Further studies are required to document the clinical consequences of this finding, for example in severe asthmatic patients.

Perez Puigb6 A et al. "Preliminary Report: An Alternative Therapy in the Management of Acute Asthma." Revista Venezolana de Alergia, Asma e Immunologia 2000; Vol. 2(2) (original in Spanish), available at <http://infomedonline.org.ve/bibliotecalRevistas/alergia/alv22000art4.pdf> (as of May 5, 2006).

ABSTRACT

In the treatment of acute asthma short acting beta agonists alone or in combination with steroids (oral or inhaled) have been employed. New bronchodilators with an improved pharmacological spectrum make the physician aware of possible and interesting avenues to be explored in the management of asthma. Twenty four asthmatic patients of both sexes and with variable degrees of airway obstruction (mean of 49% of predicted Peak Flows) presenting to the emergency room with an acute wheezing episode were evaluated clinically and with Peak Flow measurements before administration of 12 mcg of Formoterol (Foradil R capsule) diluted in 2 ml of saline sterile solution by nebulization. Peak Flows were measured again at 5 and 30 minutes showing a significant ($p < 0,0001$ paired t student test) improvement in mean peak Flows of 44,6% and 66,3% respectively. This study suggest a new way to administer Formoterol and induces further research that may help delineate its possible role in the acute management of asthma.

Respir Med. 2001 Aug; 95 Suppl B:S21-5.

Formoterol in clinical practice--safety issues.

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While Short-acting beta2-agonists are seen as the cornerstone of treatment as relief medication for asthma, current guidelines recommend long-acting beta2-agonists as maintenance therapy in combination with inhaled corticosteroids in patients with moderate to severe asthma, poorly controlled on present treatment. Although evidence has shown that formoterol, with its fast- and long-acting profile, is effective when used both as regular and as-needed therapy in all types of asthma, there has been some concern about the potential of beta2-agonists with long-acting profiles to produce side effects with a longer duration than seen with short-acting beta2-agonists. Also, where formoterol is used as needed, a higher total daily dose would be anticipated than when taken twice daily for regular maintenance therapy and this again has led to some concern. In a number of studies, formoterol has been shown to be well tolerated, and although systemic effects expected with this class of drugs did occur, formoterol had significantly less effect on serum potassium, pulse, blood pressure, cardiac frequency and QT interval compared with terbutaline. In addition, the duration of effects was equivalent to that observed with terbutaline and salbutamol and the relative therapeutic index of formoterol compared with salbutamol was found to be 2.5. Furthermore, studies looking at long-term use of formoterol have shown there is no reduction in bronchodilatory effect, and thus, no development of tolerance. In conclusion, formoterol is well tolerated in high doses, producing side effects typical of its class, but with a duration no longer than occurs with short-acting beta2-agonists. These observations, and the lack of tolerance development, suggest that formoterol may be appropriate treatment for patients with asthma of all types and severities on an as-needed basis or as regular treatment.

Clin Ther. 2002 Dec;24 (12):2077-87.

A randomized, double-blind, single-dose, crossover clinical trial of the onset and duration of protection from exercise-induced bronchoconstriction by formoterol and albuterol.

Shapiro GS, Yegen U, Xiang J, Kottakis J, Della Cioppa G.

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BACKGROUND: Inhaled short-acting beta (2)-adrenoceptor agonists are the most commonly used treatment for the prevention of exercise-induced bronchoconstriction (EIB). Formoterol, a long-acting beta (2)-adrenoceptor agonist, has been demonstrated to provide protection from EIB, although the onset and duration of this protection have not been defined.

OBJECTIVE: The purpose of this study was to determine the onset and duration of the protective effect of a single dose of inhaled formoterol powder against EIB, comparing them with the effect of a single dose of placebo and albuterol administered via metered-dose inhaler (MDI).

METHODS: In this double-dummy, 4-way crossover study, patients received single doses of formoterol (12 and 24 microg) via a powder inhaler, albuterol by MDI (180 microg), and placebo. Exercise challenge tests (ECTs) were conducted at 15 minutes and at 4, 8, and 12 hours postdose. Pulmonary function studies (forced expiratory volume in 1 second [FEV(1)] and peak expiratory flow rate) were performed before and after each exercise challenge.

RESULTS: Twenty adolescent and adult patients (mean age, 23.8 years; range, 13-41 years; 9 male, 11 female) with asthma were enrolled in the study, and 17 completed all 4 treatment sequences. Compared with placebo, both doses of formoterol produced significantly greater inhibition of FEV(1) decreases at all time points ($P < 0.01$). There were no significant differences in efficacy measures between the 2 formoterol doses throughout the study. The exercise-induced decrease in FEV(1) after albuterol treatment was significantly reduced compared with placebo only at 15 minutes after dosing ($P < 0.05$). Formoterol and albuterol exhibited a similar rapid onset of action (< 15 minutes), but formoterol continued to protect patients against EIB for at least 12 hours ($P < 0.01$), whereas albuterol was no longer clinically effective by the 4-hour ECT.

CONCLUSIONS: Formoterol and albuterol, given as single-dose inhalations, both provided protection from EIB within 15 minutes in this group of patients. The bronchoprotection afforded by formoterol lasted up to 12 hours, whereas that of albuterol was no longer significant by 4 hours.

Allergy. 1995 Aug; 50(8):657-63.

Inhaled formoterol dry powder in the treatment of patients with reversible obstructive airway disease. A 3-month, placebo-controlled comparison of the efficacy and safety of formoterol and salbutamol, followed by a 12-month trial with formoterol.

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Department of Pulmonary Medicine, Copenhagen University Hospital Gentofte, Denmark.

Inhaled formoterol is a potent selective beta 2-agonist with rapid onset and at least 12-h duration of bronchodilation. The aim of the study was to compare the bronchodilating effect of inhaled formoterol dry powder (dp) 12 micrograms b.i.d. with salbutamol dp 400 micrograms q.i.d. and placebo in patients with reversible obstructive airway disease (ROAD). The study design consisted of a closed 12-week double-blind, placebo-controlled, multicenter trial followed by an open noncomparative, multicenter, 12-month follow-up trial, in which the tolerability of formoterol.dp was assessed. A total of 304 patients (146 men, 158 women) aged 18-79 years, ill during 0.1-64 years, were randomized. No demographic or baseline differences were found among the different treatment groups. The bronchodilating effect of formoterol, assessed by morning premedication PEFr, was significantly superior to placebo ($P < 0.0001$) and salbutamol ($P < 0.0001$). Efficacy was maintained during the open follow-up study with 12 micrograms b.i.d. in most of the patients. A few patients, however, needed 24 micrograms b.i.d. to control their ROAD. Formoterol 12 micrograms b.i.d. significantly reduced morning and evening asthma symptoms and sleep disturbances, and reduced significantly the need for rescue medication. The tolerability of the three treatment groups was comparable. In conclusion, formoterol 12 micrograms dp b.i.d. was significantly superior to both salbutamol 400 micrograms dp q.i.d. and placebo, and reduced asthma symptoms significantly. Overall, formoterol showed a tolerability profile comparable to that of salbutamol, and no tachyphylaxis was observed during 1 year of treatment.

I believe that levalbuterol is effective in medicare patients with COPD, especially older patients with COPD. It is very effective.

Michael A. Matthay MD
Professor, University of California, San Francisco

January 19, 2007

Centers for Medicare and Medicaid
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VIA ELECTRONIC MAIL

NCA Tracking Sheet for Nebulized Beta Adrenergic Agonist Therapy for Lung Diseases (CAG-00354N)

Dear Ms. Spencer;

Pacific Pulmonary Services (Pacific Pulmonary) is providing the following comments regarding the National Coverage Analysis (NCA) for Nebulized Beta Adrenergic Agonist Therapy for Lung Diseases (CAG-00354N) proposed by The Centers for Medicare and Medicaid Services (CMS) dated December 20, 2006 and effective through January 19, 2007. The NCA references recent concerns regarding the determination of the appropriate use of nebulized beta andrenergic agonist therapy, specifically levalbuterol, for the treatment of lung diseases. It is our understanding that this NCA seeks to continue the collection and evaluation of relevant clinical data and perspectives on the use of nebulized beta andrenergic agonists that was initiated by the Local Coverage Determination (LCD) for Nebulizers; No. DL 5007 proposed by Trust Solutions, LLC dated March 1, 2006 and effective January 1, 2006. At the time, the LCD proposed that levalbuterol payment (codes J7612 or J7614) will be reimbursed at the allowance for albuterol (J7611 or J7613), and a non-compounded unit dose preparation (J7620) will be reimbursed based upon the allowances for the drug's individual components. The drugs (Xopenex and Duoneb, respectively) that will no longer be reimbursed based on their 'average sales price' data if the LCD is implemented are brand name drugs that may not be lawfully substituted for the drugs that are associated with the proposed reimbursement.¹ As such, Pacific Pulmonary has updated and ammended our original comments that were provided in response to the Trust Solutions, LLC LCD in response to this new NCA comment period. These revised comments are timely submitted.

Pacific Pulmonary is a home oxygen, oxygen equipment, sleep therapy and inhalation medication pharmacy DMEPOS provider with more than twelve years' experience in supplying the Medicare program and its beneficiaries with superior products and personal in-home services. The company serves more than fifty thousand Medicare beneficiaries from over one hundred local field service centers located in fifteen states, and its DMEPOS service centers are accredited by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). Pacific Pulmonary maintains pharmacy operations in Tempe, AZ from which is serves more than twenty thousand patients annually, a majority of which are Medicare beneficiaries. Three out of every four of these patients suffer from Chronic Obstructive Pulmonary Disease (COPD) which is the fourth leading cause of death in the United States. In addition to advanced COPD, many of our patients suffer from additional co-morbidities including, congestive heart failure, diabetes, Alzheimer's and dementia. In sum, the vast majority of our patients are elderly, mentally and physically frail, and suffer from multiple chronic illnesses. They are some of Medicare's most vulnerable beneficiaries.

Providing inhalation medications and quality patient care in the home setting to patients who suffer from the debilitating effects of COPD is a primary means of controlling the symptoms of this chronic disease in a cost effective manner. The treatment of these patients at home with nebulized inhalation medications is a medical management procedure that is frequently prescribed by physicians as a primary means of controlling symptoms of this chronic disease. Empirical evidence suggests that, for patients with advanced respiratory disease, compliant use of nebulized beta andrenergic inhalation medications results in increased quality of life and reduces the incidence of acute exacerbations of respiratory illness, and thus also decreases the need for costly emergency room visits and hospitalizations.

Background and Overview

Pacific Pulmonary has been providing respiratory drugs to its home-based patients since 1993. Pacific Pulmonary formerly compounded more than 100 different combinations of oral inhalation medications, primarily bronchodilators and anti-inflammatory medications, because of wide-spread demand for specialty formulations² Compounding was required in order to provide combination drugs in a single dose for those patients who required more than one drug in several different doses each day, and for those patients who were either allergic or resistant to commercially available doses or diluent components. In order to dispense these inhalation medications in a safe and efficacious manner in compliance with observations received from United States Food and Drug Administration ("FDA"), Pacific Pulmonary made significant investments in sterile pharmaceutical compounding pharmacy operations. Specifically, the FDA exerted significant enforcement pressure on Pacific Pulmonary and other respiratory pharmacies to limit compounding and dispense commercially available unit dose vials where available. *See*, Guidance for FDA Staff and Industry, Compliance Policy Guides Manual, Sec 460.200, Pharmacy Compounding. <http://www.fda.gov/cder/pharmcomp/default.htm>; posted 6/17/2002. The FDA's website still contains a number of warning letters that, read individually and together with CMS policies, actively promote the dispensing of commercially available unit dose medications wherever possible, including premixed albuterol and ipratropium (Duoneb) and unit dose levalbuterol (Xopenex).³

Pharmacies have responded to FDA and CMS policies that both encourage the dispensing of commercially available manufacturer-filled vials, with the result that physicians and Medicare beneficiaries with COPD have become highly dependent on the availability of manufactured single-dose combination of albuterol and ipratropium and levalbuterol inhalation solutions. Ironically, by promulgating the LCD, CMS is undermining the decade-long efforts of its sister agency to move the Medicare population to commercially manufactured drugs, because the FDA views the commercial product as being more stable and less likely to suffer from undetected contamination or human error.

Pacific Pulmonary is therefore both surprised and gravely concerned that CMS and its contractors are doing an abrupt reversal of direction by *discouraging* the use of commercially available medications by radically under reimbursing two popular, unique brand name medications. We strongly believe that gross under reimbursement proposed for two frequently-prescribed drugs, combined with cuts in the dispensing fees that are too low to support a return to sterile compounding of chemically equivalent drugs, will result in a near-immediate and far-reaching negative impact on beneficiary access. In addition to believing that CMS may not lawfully create and apply a "less costly alternative" pricing methodology to drugs whose prices are established by Congressional fiat, we suggest that it is unwise to do so precipitously and without further consideration of access issues.

We are responding again to the invitation to comment on this subject, this time under the auspices of the recent CMS NCA, and discuss the following points at more length below:

I. Under the Medicare Prescription Drug Improvement and Modernization Act ("MMS"), Medicare part B drugs are reimbursed at Average Sales Price plus six percent (ASP+6%). The Trust Solutions' proposed reimbursement methodology is not calculated using ASP +6% for these drugs, and is therefore unlawful under the MMA. Further, the effect of the Trust Solutions' proposal is to impose a "functional equivalence" standard ("less costly alternative" pricing) upon Part B covered outpatient drugs, also expressly prohibited by the Medicare Modernization Act. In addition, the manner in which CMS and its contractors propose to apply the rule undermines Congressional legislation aimed at encouraging early generic competition against popular brand drugs.

II. The FDA has sole responsibility for deciding whether a drug is unique and necessary when compared to other drugs on the market. CMS and its contractors cannot usurp the role of the FDA and determine that a drug is not clinically distinguishable from other drugs or drug combinations, particularly after the FDA has determined that it is a "new" drug that must be independently evaluated for efficacy.

III. CMS's proposed use of a "less costly alternative" rule is inappropriate and ineffective unless the prescribing physician and the dispensing provider have aligned interests and are effectively employed as a "gatekeeper" with respect to the cost/benefit analysis, and/or the dispensing provider has a legal right to dispense a more cost efficient product, e.g., a generic drug that is interchangeable. In this case, the retail pharmacy presented with a prescription for either of the drugs is held hostage: it may not dispense any other drug under pharmacy law, and it will not be paid for its costs under the proposed LCD. This, combined with Medicare supplier standards and mandatory assignment, will create a significant barrier to access for these drugs for all citizens who are served by retail pharmacies that serve Medicare Part B.

IV. In the event these recommendations are enacted on a nationwide basis, the LCD will reduce reimbursement for Duoneb by an estimated seventy-three percent (73%) and Xopenex by an estimated ninety-five percent (95%) below current Medicare payment levels.⁴ As a result, the reimbursement rates for both drugs would be far below the pharmacist's acquisition cost, meaning that pharmacies and suppliers will be unable to dispense these drugs to Medicare beneficiaries once the proposed changes are implemented.

I. The Proposed Reimbursement Methodology is Unlawful under the Medicare Modernization Act

These drugs are FDA-approved drugs that have been and are covered by Medicare Part B. As a matter of law, neither Trust Solutions⁵ nor CMS may lawfully: 1) Reimburse a drug at an amount that is not based upon sales data reported for the drug as mandated by Congress; or 2) Apply a functional equivalence standard to a Part B outpatient drug that does not have an FDA-rated generic.

Reimbursement for drugs under Medicare Part B has historically been established by statute, most recently under the Medicare Modernization Act ("MMA") Relevant Part B reimbursement provisions are codified as section 1842 (o) of the Social Security Act.⁶ This law directs that reimbursement for inhalation drugs furnished through durable medical

equipment "is equal to"⁷ "the amount provided under section 1847A for the drug or biological."⁸

Section 1847A sets reimbursement for Duoneb and Xopenex at Average Sales Price (ASP) plus 6%.⁹ If the Secretary has reason to believe that reimbursement under ASP + 6% is too high, the government has statutory authority to adjust reimbursement consistent with widely available market price or the average manufacturer's price. Trust Solutions proposed to pay an amount that is not equal to the amount provided under section 1847A for the drugs at issue, and is undeniably not a product of any cost data collected pursuant to section 1847A.

Instead, Trust Solutions proposed that Medicare pay an amount that is equal to the ASP based price for drugs that Trust Solutions alleges are functionally equivalent to Duoneb and Xopenex in terms of use and medical necessity. However, not only does the MMA fail to give Medicare the right to base reimbursement on the ASP established for any other brand name or generic drug, it demonstrates clear Congressional intent *not* to permit further regulatory interference with the ASP pricing scheme for outpatient drugs using functional equivalency, i.e., a less costly alternative methodology, for these drugs. For example, the MMA specifically precludes the Secretary from publishing regulations that would apply a "functional equivalence standard to a drug or biological" for Part B drugs in a hospital outpatient setting unless the drug is rated as bioequivalent by the FDA.¹⁰ The proposed functional equivalents are not so rated.

Congress painstakingly designed ASP-based pricing and any further cost-containment measures in the MMA to be tied to market-based data relating to the actual cost of the drug to the provider with the intent and effect of reimbursing providers at estimated acquisition cost, while ensuring that beneficiary access to covered Part B drugs was not negatively impacted. CMS has acknowledged the supremacy of the Congressional pricing structure for drugs in promulgating the rule on when Medicare will apply inherent reasonableness, and has indicated that it will not apply inherent reasonableness to price Part B drugs, but will defer to the statutory pricing provisions of the MMA.¹¹ Significantly, even if CMS were to apply inherent reasonableness to pricing for Duoneb and Xopenex, we suspect that the application of inherent reasonableness would produce a reimbursement amount that is either roughly or exactly equivalent to the ASP + 6% price set forth under the MMA.¹²

Further evidencing the intent to reimburse drugs at market price and to ensure that beneficiaries had access to all covered outpatient drugs, Congress directed the Medicare Payment Advisory Committee to study the impact that ASP pricing has on the "quality of care furnished to individuals enrolled under part B and the satisfaction of such individuals with that care" as well as the "adequacy of reimbursement" for Part B covered drugs.¹³ Such a study, if one were conducted following implementation of the proposed LCD, would unquestionably reveal that a significant number of beneficiaries are being denied the opportunity to receive the prescribed therapy because the drug is grossly under reimbursed, which is precisely what Congress wished to prevent.

The Trust Solutions LCD, if implemented, will arbitrarily reduce reimbursement for these two drugs, the prices of which can be firmly established in accordance with the plain language of the MMA, and would reimburse the drug at a rate that is not "equal to" ASP + 6% for the drugs being reimbursed, but would instead reimburse the drugs at the ASP +6% established for different drugs. As a result, the recommendation contained in the Trust Solutions draft nebulizer LCD is more arbitrary than it first appears, since the use of generic albuterol sales data bears no relationship to the cost of Xopenex or Duoneb and there is no support in law or in logic for using

market data from one drug to establish reimbursement for another particularly where, as here, the drugs cannot be lawfully substituted.

In fact, the Trust Solutions proposal does more than merely ignore unambiguous statutory reimbursement instruction; it thwarts the efforts of Congress to weave sales-based pricing and generic preference legislation in a careful manner that is designed to encourage rapid development of generic competition that benefits all citizens - not just Medicare - by lowering market prices. Increasingly strengthened Hatch-Waxman Act provisions encourage generic drug manufacturers to challenge popular brand name patents at the earliest possible opportunity, while ASP-based reimbursement will rapidly decrease since ASP will be calculated as a weighted average of all FDA-rated generic alternatives.

The combination of the ASP-based pricing and Hatch-Waxman laws poses a powerful, lawful means of reducing costs through generic competition without discouraging drug research and innovation at any level. It is therefore dispiriting that Trust Solutions has proposed a reimbursement methodology that derails Congress' intent on the eve of a potentially successful challenge to Duoneb's patent.¹⁴ Duoneb will essentially lose its place in the market overnight before the challenge is completed, robbing the would-be generic competitors of any financial incentive to push toward market entry for a generic version of this immensely popular and effective drug. Trust Solution's arbitrary and unlawful application of a 'least costly alternative' reimbursement thus *discourages* generic competition precisely at the time Congress's legislative efforts would have brought a generic version of this innovator drug to market at a reduced cost.

II. The FDA - Not CMS or its Contractors - is the Appropriate DHHS Agency To Decide the Medical Necessity of Duoneb and Xopenex When Compared with Other Drugs

The FDA is solely responsible for determining whether a new or unique drug is safe and clinically effective for distribution within the United States for its labeled purposes. The FDA exercises this authority through its New Drug Application (NDA) and approval processes. Both Xopenex and Duoneb were determined by the FDA to be a "new" drug within the meaning of Section 505 of the FDCA, and were required to file an NDA and submit to the long and costly approval process. The FDA required that each drug file and NDA because the agency determined that the drugs were not clinically equivalent to any other drug already on the market, including albuterol and ipratropium bromide, either individually or together.¹⁵

CMS in general, and Trust Solutions in particular, possess no authority to substitute their own less-informed judgment regarding clinical distinctions between drugs for that of the FDA. While it is clear that the meta-survey of published clinical evidence Trust Solutions relied upon in concluding these drugs are not 'medically necessary' as compared with albuterol and ipratropium was neither complete in scope, nor conclusive in its findings, it is a matter of record that the FDA approved both drugs as being both unique when compared to the drugs named by Trust Solutions, and effective (i.e., "medically necessary") for treating patients suffering from chronic respiratory conditions.

In the opinion of Pacific Pulmonary, and based upon patient and physician based evidence, the FDA was not in fact wrong in its judgment that both of these drugs are an improvement over the existing albuterol or dual-drug therapies that Trust Solutions is citing as equivalent alternatives for a significant portion of the Medicare population. With respect to Xopenex, our pharmacists have found that physicians prescribe it deliberately in lieu of racemic albuterol for a small (approximately 10%) and specific cohort of our patients - those that suffer from documented co-morbid or underlying cardiac conditions, or who cannot tolerate racemic

albuterol. While Trust Solutions' LCD suggests that Xopenex cannot be medically differentiated from albuterol for all Medicare patients, empirical evidence suggests that physicians and patients disagree. This would suggest that, at the very least, CMS should adopt a policy that would make Xopenex available to those beneficiaries for whom the prescribing physician has *considered* the use of racemic albuterol and has determined that levalbuterol is a more appropriate therapy for reasons such as, but not limited to the following: albuterol has proven problematic; those who have diagnoses that suggest susceptibility to racemic albuterol's negative side effects; or those who have demonstrated resistance to racemic albuterol.

With respect to the medical necessity of commercially available combination albuterol and ipratropium (Duoneb), the medical necessity for a single, combined drug has largely been defined by the condition (both physical and mental) of the beneficiary. In all cases, the drugs will take twice as long to administer and this factor alone will decrease compliance. Patients who were taking three ampules a day at 7-10 minutes per ampule will find the inconvenience of administration time doubled to as much as an hour a day. More importantly, however, beneficiaries who are easily confused or who have visual impediments are frequently discovered to have inadvertently self-administer multiple doses of one drug and miss doses of the other, a problem that is often not identified until the beneficiary has mis-dosed for a month. The result can be drug intoxication with potentially severe side effects for one drug, while under dosing for the other drug. This unhealthy phenomenon is particularly prevalent when a medication regimen is changed.

Particularly for those beneficiaries who have been prescribed Duoneb, Pacific Pulmonary expects deleterious pharmacologic effects for beneficiaries who will no longer receive single dose ampoules of the combined drugs due to confusion and a belief that the vials are interchangeable.¹⁶ The imposition of a rule that will negatively impact the quality of life of the beneficiary and reduce compliance and accurate dosing for a significant number of beneficiaries, seems reckless and ill advised when the Duoneb patent is under challenge and the benefits of this convenient drug in generic form and at generic prices may materialize in a matter of months under existing legislated provisions.

We respectfully submit that CMS nor Trust Solutions may not lawfully override or usurp the FDA's authority to decide whether one drug is a clinically distinguishable from another, or to apply a functional equivalence standard unless the FDA has rated the drugs as bioequivalent. Even if Trust Solutions were so authorized, it is inappropriate for Trust Solutions or CMS to give unfettered license to contractors to make coverage determinations that restrict beneficiary access to an approved drug in the absence of sound policies and controls on when and how the determination is made, such as the guidelines that have been promulgated for the application of Inherent Reasonableness.

III. CMS's Use of a "Less Costly Alternative" Cost Containment Policy is Inappropriate where the Dispensing Provider is Legally Prohibited from Dispensing the Less Costly Alternative, and Will Create Barriers to Access

The successful implementation of a less costly alternative policy in health care delivery is predicated on the fact that the participating provider billing the program has significant control over the recommendation or choice of the item being prescribed. The less costly alternative policy proposed in this LCD policy, in order to be implemented in any manner short of absolute chaos, would require that Xopenex and Duoneb be interchangeable with the generics used as the reimbursement benchmark. If that were the case, a pharmacist who was presented with a

prescription for either drug could lawfully dispense the drug for which he or she would receive reimbursement.

This is not the case for these drugs. A pharmacist who seeks to fill a prescription for Duoneb with two different drugs or who substitutes albuterol for Xopenex will be in violation of FDA and state pharmacy laws. Neither Xopenex nor Duoneb is FDA-rated as bioequivalent to albuterol, or albuterol and ipratropium, which Congress has indicated is the required predicate for reimbursement at functional equivalence (less costly alternative) or as a multiple source drug (using price data from a generic) under sections 662 and 303 of the MMA, respectively. Until and unless they are lawfully rated as bioequivalent, a pharmacist may not legally dispense the drugs that Medicare deems are the functional equivalent or least costly medically necessary alternative - a fact that, standing alone, should be sufficient reason to rethink this coverage determination.

We neither acquiesce nor argue that a less costly alternative policy is lawful, but respectfully submit that it has practical limitations and should never be employed where the prescribers and the providers are not one and the same. Unlike previous applications of the functional equivalent or less costly alternative reimbursement caps, where the person prescribing the drug is the same person who is submitting a claim for reimbursement,¹⁷ Trust Solutions is applying a "less costly alternative" reimbursement rule to a drug that is prescribed by one provider and dispensed and billed by another.

The field implications for pharmacists are staggering. Medicare cannot reasonably expect pharmacists to dispense Duoneb and Xopenex and accept reimbursement that is 27% and 3% of the current ASP + 6% reimbursement, respectively. Thus, when presented with a prescription, at best, treatment will be delayed while physicians are asked to assume yet another unfunded administrative burden associated with treating Medicare patients and to re-issue prescriptions for drugs that they judged were not optimal when they first wrote the prescription. At worst, patients will be presented with Advance Beneficiary Notices and be required to pay for drugs (or go without if their physicians cannot be reached to authorize the change, and they do not have the ability to pay.)

The beneficiary access problem will likely be multiplied tenfold wherever Medicare Part B utilization is shifted from specialty mail-order respiratory pharmacies to walk-in retail pharmacies as a result of decreased in-home supplier participation, as retail pharmacies are less suited to handle the issues presented by the Trust Solutions' proposal. Pacific Pulmonary believes CMS may be relying upon these retail pharmacies as potential providers of cost-effective delivery of inhalation therapy in the event that the anticipated inhalation medication access issues become problematic in the coming year. We believe that the majority of retail pharmacies do not understand (nor do they fulfill) the basic requirements for a Medicare Part B provider of inhalation medications. They do not have, and do not intend to develop or support, the infrastructure that CMS requires to serve the at-home population.

A 2005 internal blind survey conducted by Pacific Pulmonary of 120 retail pharmacies in 43 cities in 15 states¹⁸ that included 11 chain pharmacy systems that CMS will easily identify as serving a majority of the citizens in this country,¹⁹ demonstrated conclusively that few standard retail pharmacies are prepared to work with beneficiaries if their prescribed drugs require acceptance of assignment under Part B, as is the case with these drugs. For example, the survey revealed that 96% of the chain pharmacies either do not directly bill Medicare for anything other than diabetic supplies, or do not know whether they would accept assignment, or expressly require the patient to submit bills to Medicare Part B.²⁰ None of the pharmacies suggested they

would provide advanced notice to beneficiaries that the drugs might not be reimbursed to 80% of the amount allowable.

Even if retail pharmacies become educated regarding the Part B issues, a pharmacist presented with a walk-in prescription at 6:00 p.m. is held hostage between a prescription that: 1) he will not be reimbursed for; 2) he cannot legally provide a substitute drug; 3) is written by a physician that cannot be reached to change the prescription; and 4) is needed by a beneficiary who is unaccustomed to paying and may be unable to pay.

IV. If the LCD is Implemented, Duoneb and Xopenex Will be Unavailable to the Vast Majority of Medicare Beneficiaries, Resulting in Negative Health Outcomes for Beneficiaries and Significantly Increased Acute Care Expenditures for Medicare

The conclusions stated in the draft LCD do not accurately reflect the clinical perspectives and prescribing habits of many of the prescribing physicians whom we serve. Predicated on our experience serving thousands of Medicare beneficiaries who use these drugs daily, we believe the proposed changes will negatively impact their compliance with their respiratory medication prescriptions.

In the case of Duoneb, the least costly alternative would be separate vials of 2.5mg of generic albuterol and .5mg of generic ipratropium. For Xopenex, the least costly alternative would require a substitution of 1.25 mg of generic albuterol, as there is no commercially available generic equivalent to Xopenex.

Pacific Pulmonary has the following concerns regarding substitutions for each drug, which we address separately:

A. Duoneb: The functional equivalent will increase patient non-compliance due to longer treatment times, which will in turn lead to the need for acute care treatment for preventable episodic events. Requiring patients to mix and inhale two separate vials of albuterol and ipratropium for each treatment doubles the volume of liquid that must be nebulized, and thus will double treatment time. While this sounds as if it is a modest inconvenience, even under ideal circumstances, our patients struggle to remain compliant with their inhalation medications. Many of these patients have been prescribed inhalation treatments three or more times per day, so doubling treatment time has an immediate, negative impact on their day-to-day lives and dramatically increases their resistance to the process.

Moreover, roughly 50% of our patients are immediately non-compliant, even when receiving pre-mixed medications such as Duoneb, due to factors such as confusion, treatment inconvenience, low tolerance for side effects etc. Again - this is not incidental: non-compliance in this patient base is significant in number and severe in consequence - often resulting in unnecessary and expensive acute care episodes.

B. Duoneb: Risk of mis-dosing.

In addition to unnecessarily increasing the risk of non-compliance, the burden of mixing separate vials of albuterol and ipratropium significantly increases the risk that patients will over or under-dose either medication. Our patient population is elderly, physically frail, often visually impaired, and in many cases, prone to confusion. Requiring patients to mix different inhalation medications several times each day instead of dispensing a simple regimen involving a commercially available pre-mixed alternative in the form of Duoneb is substandard medical care.

C. Xopenex: No commercially available equivalent.

Xopenex is a specialized inhalation therapy that, in the case of Pacific Pulmonary, is prescribed for approximately 10% of our patients - specifically - those that suffer from comorbid or underlying cardiac conditions, or who cannot tolerate generic albuterol. The concern regarding Xopenex is very straightforward - there is no commercially available generic equivalent to Xopenex. Patients will be forced to use generic albuterol, *which for the majority of these patients is not an acceptable substitute.*

D. Xopenex: Increase in negative side-effects and cardiac considerations, increasing non-compliance:

For those patients who cannot tolerate generic albuterol - which for Pacific Pulmonary represents more than 25% of our patients who are on Xopenex - the consequences are noncompliance, which in turn leads to preventable acute care episodes. For those patients who suffer from cardiac co-morbidities or are at risk for underlying cardiac conditions, Xopenex is the front line drug of choice. For these patients - their physicians, often specialists such as cardiologists and pulmonologists, are making the initial determination that Xopenex is the best option for the patient.

Conclusion

Pacific Pulmonary believes the practical consequences of this recommendation will be that Duoneb and Xopenex will no longer be available to the vast majority of Medicare beneficiaries and this will require a substitution of separate vials of albuterol and ipratropium. Medicare patients will effectively lose access to the unique therapeutic properties and effects of these two drugs and be forced to accept least costly generic alternatives that we believe do not provide equivalent or acceptable treatments. It is highly likely this will have a negative impact on patient compliance. Increasing rates of patient non-compliance will likely result in the exact same outcomes we see today in our non-compliant patient base - a dramatic, and largely preventable increase in the utilization of costly acute care including unplanned physician and emergency room visits and hospitalizations.

In addition, if the Trust Solutions proposed changes are implemented, Medicare beneficiaries who are dependent upon these two self-administered inhaled medications will be forced to change their prescribed medication regimens almost overnight, and many beneficiaries will suffer an interruption in their medication regimens. The impact on these beneficiaries is an unwarranted suspension of their right to receive drugs that are covered as a matter of law, both generally and specifically, by Medicare Part B. We respectfully submit that the proposed reimbursement change represents an unlawful usurpation of Congress' exercise of authority over drug pricing; impinges upon the authority granted to CMS's sister agency, the United States Food and Drug Administration (FDA); has the effect of extending the use of "least costly alternative" beyond its lawful or practical application and is, simply stated, bad policy-making that will lead to unnecessary confusion, complication, and needless risk to the Medicare population.

Pacific Pulmonary respectfully requests that CMS work with industry to maintain a coverage policy that will balance the need to preserve access with the need to ensure that the Medicare program receives value for the items and services that it purchases. Specifically, Pacific Pulmonary recommends that CMS adopt the following recommendations with respect to the recent NCA and the Trust Solutions, LLC LCD: Maintenance of the ASP+6% cost basis for the reimbursement of both Duoneb and Xopenex in order to preserve access for these important

medications for Medicare beneficiaries. Inasmuch as policy decisions must be made by CMS in order to protect access, we are optimistic that the agency will act in a fair and balanced manner, and we stand ready to assist CMS in this important effort

Sincerely,

Chris Kane
Vice President of Government Affairs

cc: Herb Kuhn, CMS
Leslie Norwalk, Esq., CMS

Exhibit A

Transcript of verbal comments presented by Pacific Pulmonary Pharmacist in Charge, Mr. Duane Angulo, Pharm D, J.D. , at both the TrustSolutions Teleconference for the Draft Nebulizer LCD Open Meeting on April 26, 2006 the IntegriGuardIEDS Region D PSC Open Door Forum for the Draft Nebulizer LCD on April 28th, 2006

PPS DMERC Comments Outline

Duane Angulo, Pharmacist in Charge (PIC)

Preamble:

Thank you for the opportunity to participate in today's meeting. My name is Duane Angulo, and I am the Pharmacist in Charge for Pacific Pulmonary Services (which, in the interest of time, I will refer to as PPS in the remainder of my presentation).

I am providing my comments today on behalf of both PPS and the American Association of Homecare.

A significant number of the Medicare beneficiaries under our care have been prescribed either Duoneb or Xopenex as their primary inhalation medication therapy. Please note that my comments are not focused on studies published in peer reviewed journals or a meta-review of clinical data....rather, they draw from my experience supporting these beneficiaries and their prescribing physicians.

PPS Operations:

Before I begin - I would like to provide a quick overview of PPS:

We are a super regional provider of home respiratory therapy, including oxygen and inhalation medications, serving more than 50,000 patients in 15 states. We maintain closed-door pharmacy operations in Bakersfield, CA and Tempe, AZ.

As the PIC for PPS, I oversee pharmacy operations that support over six thousand physicians and each month we communicate with more than ten thousand Medicare beneficiaries who require inhalation medications.

On average, our patients are 75 years old, while 35% are over 80 years of age.

3 out of every four of these patients suffer from Chronic Obstructive Pulmonary Disease (COPD) - many with additional co-morbidities including, Congestive Heart Failure, Diabetes, Alzheimer's and Dementia.

Bottom line - the vast majority of our patients are elderly, mentally and physically frail, and suffer from multiple chronic illnesses. They are some of Medicare's most vulnerable beneficiaries.

Comments:

As a professional pharmacist and PIC for PPS - I firmly oppose the recommendations contained in the draft nebulizer LCD that propose reducing the reimbursement for both Duoneb and Xopenex to their least costly alternatives.

In the case of Duoneb, the least costly alternative would be separate vials of 2.5mg of generic albuterol and .5mg of generic ipratroprium.

For Xopenex, the least costly alternative would require a substitution of 1.25 mg of generic albuterol, as there is no commercially available generic equivalent to Xopenex.

I will address my concerns regarding substitutions for each drug separately:

Duoneb:

Increase in non-compliance due to longer treatment times, which leads to preventable acute care episodes.

Requiring patients to mix separate vials of albuterol and ipratroprium for each treatment will double their treatment time, at a minimum. While this sounds as if it is a modest inconvenience, it must be placed in the proper perspective. Many of these patients have been prescribed inhalation treatments 3 or more times per day, so doubling their treatment time has an immediate, negative impact on their day-to-day lives.

Additionally, in ideal circumstances, our patients struggle to remain compliant with their inhalation medications:

Roughly 50% of our patients are immediately non-compliant, even when receiving pre-mixed medications such as Duoneb, due to factors such as confusion, treatment inconvenience, low tolerance for side effects etc. Again - this may sound incidental, but the consequences of non-compliance in this patient base are severe - most often resulting in unnecessary and expensive acute care episodes.

I believe the practical consequences of your recommendation will be that Duoneb will no longer be available to Medicare beneficiaries and this will require a substitution of separate vials of albuterol and ipratroprium.

It is highly likely this will have a negative impact on patient compliance. I would like to share a recent patient experience with you to illustrate my concern:

Duoneb patient anecdote #1

Elderly gentleman initially on a generic compound of albuterol and ipratroprium with a different pharmacy provider.

The gentleman switched physicians, and his new doctor prescribed Duoneb and placed him under the care of our pharmacy. While he was on our service using Duoneb, he was compliant with his medications and remained stable in his home environment. A move to a new location forced him to change physicians again - and, unfortunately, his new physician informed him the Duoneb was too expensive and he could get the same benefit from generic medications, so he changed his Rx to two separate components of albuterol and ipratroprium.

Regrettably, the gentleman struggled with the requirement that he mix his medications, eventually grew too frustrated and ceased taking his treatments all together - with predictable results. He ended up requiring treatment at an urgent care center - where - the doctor changed his

prescription back to Duoneb. I am happy to report that this gentleman is back home and stable again.

Risk of mis-dosing.

In addition to unnecessarily increasing the risk of non-compliance, requiring patients to mix separate vials of albuterol and ipratropium **significantly increases the risk that patients will over or under-dose either medication**. As I explained earlier, our patient population is elderly, physically frail and in many cases, prone to frequent bouts of confusion. Requiring them to mix their inhalation medications several times each day, while withholding a commercially available pre-mixed alternative in the form of Duoneb, defies common sense. Again, a recent patient anecdote illustrates my point:

Duoneb patient anecdote #2

An elderly woman who is her husband's caregiver. She suffers from moderate Alzheimer's disease. He was prescribed separate vials of albuterol and ipratropium, which she was responsible for administering to him several times a day. We began to notice discrepancies in the number of vials they had remaining each month and after investigating, determined that she had become confused about how to administer his medications, so had resorted to using just one medicine, not both. This led to a deterioration, which resulted in the gentleman being hospitalized. The hospitalist recognized the problem and changed the gentleman's prescription to Duoneb. He is now doing significantly better, and she communicated to me that it has reduced her stress and improved her quality of life.

Xopenex

No commercially available equivalent.

Xopenex is a specialized inhalation therapy that, in the case of PPS, is prescribed for less than 10% of our patients - specifically - those that suffer from co-morbid or underlying cardiac conditions, or who cannot tolerate generic albuterol.

My concern regarding Xopenex is very straightforward - there is no commercially available generic equivalent to Xopenex. Patients will be forced to use generic albuterol, **which for the majority of these patients is not an acceptable substitute**.

Increase in negative side-effects, increasing non-compliance:

As I mentioned above - PPS dispenses Xopenex to two distinct types of patients - those at risk for cardiac complications, and those who for any number of reasons have a documented intolerance for generic albuterol.

For those patients who cannot tolerate generic albuterol- **which for PPS represents more than 25% of our patients on Xopenex** - the consequences are non-compliance, which in turn leads to preventable acute care episodes. Again - a patient anecdote provides the best illustration:

Xopenex patient anecdote #1

An elderly woman who was taking full strength albuterol. As she described to me, the side effects were so severe she felt as if she was jumping out of her skin. Her tolerance for this was so low;

she stopped taking the medication outright, and was hospitalized for respiratory distress. The hospitalist put her on Xopenex, which she was able to tolerate, and maintain her treatments, allowing her to be stable at home. In one of my follow-up calls to her, she mentioned that the generic albuterol left her feeling so bad that she would rather die than take it. And she was serious.

Cardiac considerations:

For those patients who suffer from cardiac co-morbidities or are at risk for underlying cardiac conditions, Xopenex is the front line drug of choice. For these patients - their physicians, often specialists such as cardiologists and pulmonologists, are making the initial determination that Xopenex is the best option for the patient. In my role as the PIC, I have the opportunity to speak with these physicians on a regular basis:

1 Specifically, "The medical necessity of levalbuterol (Xopenex) compared to albuterol has not been established. Therefore ...payment will be based on the allowance for the least costly medically appropriate alternative, J7611 or J7613 (generic albuterol) respectively. "The medical necessity for administering albuterol and ipratropium in a non-compounded, combined unit dose preparation (Duoneb) has not been established.... Therefore ...payment will be based on the allowance for the least costly medically appropriate alternative - 2.5 units of J7613KO (generic albuterol) and 0.5 units of J7644KO (generic ipratropium)."

2 The LCD would also limit reimbursement for a number of the specialty combinations that were and still are requested by Pacific Pulmonary's physician referral sources.

3 For example, *RespiCare Group of Puerto Rico; SJN -05-02, December 20, 2004; Lincare, 2005-NOL-06, December 9, 2004; MedMart Pulmonary Services, September 30, 2002.*

4 Pacific Pulmonary's estimates are based on current Medicare payment rates.

5 We also note that under section 1869(f) of the Social Security Act, only carriers and intermediaries may issue local coverage determinations. Trust Solutions is a program safety contractor and is neither an entity that may independently issue an LCD, nor a subcontractor of such entity. Thus, the LCD itself is likely invalid.

6 42 USC 1395u (o)

7 § 1842 (0) (1).

8 § 1842 (o) (G) (ii).

9 Prices may also be based on a reported WAC if that number less than ASP.

10 Section 662 of the MMA. This provision prohibits the use of less costly alternative pricing for drugs that were on the market prior to the passage of the MMA. Among other things, the provision appears to have signaled Congress' disdain for Medicare's attempts to impose less costly alternative pricing on non-equivalent covered out patient drugs such as Aranesp, a competitor of the cheaper drug, Procrit.

11 *See, Medicare Program; Application of Inherent Reasonableness Payment Policy to Medicare Part B Services (Other Than Physician Services), 70 Fed. Reg. Vol. 238, p.73, 623. "(B) because of the new pricing methodology for Part B drugs established by section 303 of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (Pub. L. 108-173), we do not anticipate the need to apply the inherent reasonableness provisions to these drugs at this time; however, we are retaining our authority to apply inherent reasonableness to these drugs if the need arises."*

12 If CMS were to apply inherent reasonableness (IR) pricing rules to Duoneb and Xopenex, the new price would be based on roughly the same marketplace data and analysis as ASP pricing that is set forth in the MMA. IR does not

permit the substitution of pricing data for a *different* drug or permit the gross under-reimbursement of a covered out patient drug or service.

13 Section 303 (a) (5) of the MMA.

14 Duoneb's patent is under numerous paragraph IV challenges in the United States District Court in Los Angeles, consolidated and set for trial in June of this year. Many predict the outcome will result in the near-immediate entry of a generic competitor. Thus, Medicare appears poised to wrest a drug that fosters compliance from the beneficiaries just before the price will drop by operation of law.

15 The FDA publishes a list of drugs that have clinical equivalency, commonly referred to as the "Orange Book." Neither Duoneb nor Xopenex have any AB rated equivalent drugs. Thus, albuterol may not be legally substituted for either Duoneb or Xopenex. See, <http://www.fda.gov/cder/ob/default.htm>

16 Pacific Pulmonary Pharmacist in Charge, Mr. Duane Angulo, Phann D, J.D., detailed verbal comments and collected patient anecdotes documenting this effect at both the TrustSolutions Teleconference for the Draft Nebulizer LCD Open Meeting on April 26, 2006 the IntegriGuardLEDS Region D PSC Open Door Forum for the Draft Nebulizer LCD on April 28, 2006. A transcript memorializing Mr. Angulo's comments is attached as Appendix A.

17 For example, less costly alternative was applied in limited fashion to the chemically-equivalent drugs Lupron and Zoladex, which are purchased, administered and billed by urologists. Lupron, which is easier to administer and preferred by patients, is more costly. Where the relative additional costs to the patient and/or the convenience to the physician and patient are decided between them at the time of the physician's counsel, the decision is an informed choice made by the physician and patient. Similarly, attempts to place Aranesp at the less costly price established by a different drug with overlapping therapeutic benefits, Procrit, could be balanced by providers that both purchased and billed for the drug when the drug was administered by a hospital or during a chemotherapy session. The less costly alternative led to access problems when administered as a Part B drug in the outpatient setting. Similarly, where less costly alternative concept is devices, the supplier is presented with a generic prescription (e.g., for a "wheelchair") that will cover the dispensing of any grade chair. In such case, it is reasonable to expect the supplier to assume responsibility for assessing medical necessity issues and bearing the costs associated with any losses if the supplier overstates or under documents the beneficiary's need.

18 Brewer, Maine; Baltimore, Maryland; Rockville, Maryland; Germantown, Maryland; Raleigh, North Carolina; Hoover, Alabama; Somerville, Massachusetts; North Creek, New York; New York City, New York; Fairfax, Virginia; Alexandria, Virginia; Roswell, New Mexico; Albuquerque, New Mexico; Santa Fe, New Mexico; Rio Rancho, New Mexico; Stockton, California; Bakersfield, California; Modesto, California; West Covina, California; Studio City, California; San Gabriel, California; Monrovia, California; Visalia, California; Porterville, California; Chico, California; Paradise, California; Phoenix, Arizona; Glendale, Arizona; Scottsdale, Arizona; Peoria, Arizona; Spokane, Washington; Bellingham, Washington; Seattle, Washington; Grants Pass, Oregon; Medford, Oregon; Aloha, Oregon; Portland, Oregon; Coeur d'Alene, Idaho; Boise, Idaho; Las Vegas, Nevada; Lincoln, Nebraska; Fort Worth, Texas; Dallas, Texas.

19 Walgreens Pharmacies; CVS Pharmacies; Rite Aid Pharmacies; Longs Drugs; WalMart Pharmacies; Brooks/Eckerds; Duane Reade; Albertson's - SavOn Drugs; Safeway Foods Pharmacy; Giant Food Pharmacy (Ahold); Hy-Vee Pharmacy.

20 In addition, 98% would not ship/deliver to the homebound patient, none supplied the related equipment and 91% did not provide Part B mandated patient education and training on DME nebulizer equipment. Although it was not a structured survey question, Pacific Pulmonary respectfully suggests that few or none of the pharmacies would perform the compliance calls mandated for mail order specialty pharmacies that are designed to identify chronic non-compliance with the medication regimen that is prescribed with the intent of reducing acute care costs and the need for long term hospitalization and/or skilled nursing care.

>PUBLIC COMMENT

»

»RE: NCA: Nebulized Beta Adrenergic Agonist Therapy for Lung Diseases

»

»1/19/07

»

»To whom it may concern:

»

»Below, I make four comments or request for clarifications.

»

»First, I suggest the comment period for this NCA be extended, given
»that this NCA was removed or not available on the website for some
»indeterminate period of time earlier this week. Moreover, I recommend
»CMS send an e-mail notification to that effect on an appropriate CMS
»LISTSERV.

»

»second, I request a clarification of the scope of this National
»coverage Analysis (NCA). The NCA states, "CMS has internally

HEALTH NOTES (sun. 12107)--Four Horseman of Health policy '07 uninsured Medicare Cuts
Drugs (

»generated a formal request for a National coverage Analysis to
»determine when treatment with a nebulized beta adrenergic agonist is
»reasonable and necessary for Medicare beneficiaries with COPD". That
»statement implies review of all beta a9onists, both short and long
»lasting. However, the NCA text emphasizes an interest in nebulized
»I evalbuterol, which may lead some potential commentators to limit the
»scope of their comments.

»

»Indeed, the broader scope would be appropriate given the conclusion of
»a draft (and still pending) Nebulizer policy published by the three
»DME program safeguard Contractors
»(pscs) on March 24, 2006. That draft proposes to eliminate coverage
»for bitolerol, formoterol, and terbutaline "because there is
»inadequate support in the medical literature for administration using
»a DME nebulizer".

»

»By way of background, short-acting beta a9onists include salbutamol
»(albuterol), levalbuterol, terbutaline, plrbuterol, procaterol,
»metaproterenol, fenoterol, bitolterol mesylate.
»Long-acting beta a9onists include salmeterol, formoterol, and
»bambuterol. And, In October 2006, the FDA approved arformoterol
»(proprietary name: Brovana).

»

»Third, I request a clarification of the statement "CMS has become
»aware of concerns regarding the appropriate use of nebulized beta
»adrenergic agonist therapy for lung diseases."
»could CMS provide some discussion of those "concerns"?

»

»Fourth, I request a clarification if CMS could, under the CMS policy
»governing National Coverage Analyses (NCA) and National coverage

»Determinations (NCD) , endorse or establish claims for a drug product
»that have not been approved by the FDA, or, moreover, actually
»prohibited by the FDA.

»

»For example, xopenex (levalbuterol HCl) Inhalation solution was
»approved by the Food and Drug Administration (FDA) on March 25, 1999.
»Although the FDA concluded that xopenex was "safe and effective" per
»the approved label (see FDA Approval package, link below), the FDA
»subsequently warned the manufacturer of xopenex, sepracor, Inc., of
»Marlborough, MA, on two separate occasions, to "cease immediately"
»making certain claims that xopenex was safer or more effective than
»racemic albuterol (see links below). TO my knowledge (a fact question
»that should be independently ascertained), the FDA has not
»subsequently approved any claims of superior safety or efficacy for
»xopenex. (For a complete record, it would also be useful to know if
»sepracor has requested FDA approval of additional safety or efficacy
»claims, and on what basis; or if sepracor has funded or encourage such
»studies, published or unpublished. I suggest sepracor be directly
»asked by CMS if the company has any such additional data.)

»

»Thus, with regard to this specific NCA, could CMS establish a coverage
»policy for Levalbuterol which impliedly makes product claims broader
»than those permitted by the FDA? (clearly, the issue here is not off
»label use.)

»

»LINKS:

May 2, 2006

Paul J. Hughes, M.D.
Medical Director, DME PSC Regions A&B
TriCenturion
7909 Parkland Road, Suite 190
Columbia, SC 29223

Re: Comments: LCD for Nebulizers· Draft (DL11499)

Dear Dr. Hughes:

On behalf of the American Association for Respiratory Care (AARC), we are pleased to submit comments on the proposed revisions to the Durable Medical Equipment Program Safeguard Contractors' (DME PSCs) local coverage determination concerning nebulizers. The AARC is the national professional association representing over 41,000 respiratory therapists who treat high-risk patients with chronic conditions such as asthma and chronic obstructive pulmonary disease (COPD), including emphysema and chronic bronchitis.

In reviewing the changes to the nebulizer policies, the AARC is particularly concerned that patient access to medications prescribed by their physicians could be severely compromised. Further, based on our review of the scientific literature, we believe the finding by the DME PSCs that the medical necessity of levalbuterol has not been established is unfounded and arbitrary.

Our comments focus on two of the four items open for public comment. They are:

- Payment for levalbuterol based on the allowance for albuterol;
- Elimination of certain nebulizer drugs due to inadequate support in the medical literature for administration using a DME nebulizer.

Payment for Levalbuterol

1. The determination by the DME PSCs that the medical necessity for levalbuterol compared to albuterol has not been established is seriously flawed. An evaluation of the literature does not support the conclusion drawn by the DME PSCs that there is no therapeutic advantage of levalbuterol versus albuterol. In fact, the evidence is quite the contrary. A number of the studies cited by the DME PSCs indicate levalbuterol has significantly better outcomes than albuterol, thus demonstrating its medical necessity.

The draft nebulizer policy states the following: "The medical necessity for levalbuterol compared to albuterol has not been established." We reviewed a random number of the articles cited in the draft policy as the basis for the decision to reduce the payment level for levalbuterol to that of albuterol. While some of the articles indicate there is no comparative efficacy between the two drugs, our analysis below shows that quite a few articles support the therapeutic value of levalbuterol over albuterol. Thus, based on AARC's review of the scientific literature, we question how the DME PSCs can make such a definitive statement that medical necessity for levalbuterol compared to albuterol has not been established.

Of the eleven articles we reviewed cited in the DME PSCs' draft nebulizer policies, the following articles concluded that levalbuterol had a more positive outcome than albuterol. For example,

Truitt, Witko and Halpern¹ compared the efficacy and outcomes in patients hospitalized with chronic obstructive pulmonary disease (COPD) or asthma in a 2003 study published in *CHEST*. The study concluded that "compared with patients treated with racemic albuterol, those treated with levalbuterol required less medication, had shorter lengths of hospital stay, had decreased costs for nebulizer therapy and hospitalization, and appear to have a more prolonged therapeutic benefit. These findings support using levalbuterol as a first-line therapy for hospitalized adults with COPD or asthma."² In this study, 125 patients were treated with nebulized racemic albuterol and 109 patients were treated with levalbuterol.

Another article cited in the draft policy is an editorial³ by Leslie Hendeles⁴, PharmD and Abraham Hartzema, PhD, in which they question the claims of the findings in the Truitt, et al study described above. They state "no conclusions can be drawn about clinical advantages since the treatments were not administered in a double-blind randomized manner." The authors, neither of who are physicians, believe that the reviewers missed a fatal flaw in the study design. However, Truitt, et al responded to the editorial, taking into account each of the negative points made and refuting the comments in each case, noting that the reviewers at *CHEST* understood the study "for what it was" and standing by the peer-review process and the quality of the reviewers.

While we did not review the abstract presented by Schreck et al to the American College of Emergency Physicians in 2001 "Comparing Racemic Albuterol and Levalbuterol in the Treatment of Acute Asthma", which is noted in the draft policy, we did review a later article by Schreck and Babin appearing in the *American Journal of Emergency Medicine* in 2005,⁵ comparing emergency department (ED) admission rates of patients presenting with acute asthma who were treated with either racemic albuterol or levalbuterol. The article concluded, "Levalbuterol treatment in the emergency department for patients with acute asthma resulted in higher patient discharge rates and may be a cost-effective alternative to racemic albuterol." The results showed of the initial 736 consecutive cases, "significantly fewer admissions (4.7% vs. 15.1 %, respectively; P = .0016) were observed in the levalbuterol versus racemic albuterol group." Of the subsequent 186 consecutive cases, "significantly fewer admissions were also observed (13.8% vs. 28.9 %, respectively; P = .021) in the levalbuterol vs. racemic albuterol group." The study also stated that treatment costs were lower with levalbuterol mainly because of a decrease in hospital admissions.⁶

A study by Quinn⁷ in 2004 also points to the conclusion that "Levalbuterol is a formulation containing only the R-isomer of albuterol, and clinical trials have demonstrated that it offers therapeutic advantages over racemic albuterol". The cost effectiveness of levalbuterol derives mainly from reduced need for acute medical care and hospitalization."

The Haider⁸ study published in *Respiratory Care* in 2001 also shows a favorable outcome for levalbuterol. The study compared levalbuterol (LEV) and racemic albuterol (RAC) for the treatment of acute bronchoconstriction from primary asthma in the emergency department (ED). The data suggest, "LEV, compared to RAC, is a clinically superior bronchodilator, decreases β_2 -mediated side effects, improved clinical outcomes, and provides cost efficient asthma management in the ED." The data supporting their conclusions are, in part, the following:

- "Greater bronchodilation was achieved with lower total amounts of LEV (3 mg/patient) compared to RAC (11.5 mg/patient)";
- "LEV patients experienced decreased heart and respiratory rate suggesting resolution of hypoxia and reduced anxiety. In contrast, RAC patients showed increased heart rate and less of a decrease in respiratory care";

- "Twenty percent of RAC patients were admitted to the hospital subsequent to ED therapy, while 12% of LEV patients were admitted."
- "Length of hospital stay was 35 hours for RAC patients and 23 hours for LEV patients."
- "Despite the higher cost of LEV (\$1.54/unit dose) compared to RAC (\$0.37/2.5 mg/unit dose; \$0.60/5.0 mg/unit dose) and Atrovent (\$1.12/0.5 mg/unit dose), the total cost of bronchodilator therapy between the two groups was similar (\$4.89 and \$4.23 for LEV and RAC, respectively). This resulted from fewer LEV and Atrovent administrations necessary to achieve bronchodilation."

In a study by Handley et al in 2000⁹, which is not listed in the draft policy, a dose-evaluation of levalbuterol versus racemic albuterol was conducted in patients with asthma. According to the study, "serial pulmonary function was assessed at 15-minute intervals and mean time to onset of activity and duration of improvement of forced expiratory volume in 1 second (FEV1) were measured." The study results found levalbuterol to provide significant bronchodilatory activity and was well tolerated. "Levalbuterol 1.25 mg provided the greatest increase and duration in FEV1 improvement, whereas racemic albuterol (2.50 mg) and levalbuterol 0.63 mg provided comparable effects. The lower doses of levalbuterol were associated with a less marked effect on heart rate and potassium than racemic albuterol or high-dose levalbuterol. These data suggest that 0.63 mg levalbuterol provides bronchodilation equivalent to 2.50 mg racemic albuterol with less beta-mediated side effects."¹⁰ Another study conducted by Nowak, et al,¹¹ noted that the negative correlation between (S)-albuterol levels (racemic albuterol) and FEV1 could suggest a deleterious effect of (S)-albuterol. Larger comparative studies are warranted." In this study, after the first dose, "FEV1 changes were 56% (0.6L) for 1.25 mg of levalbuterol and 6% and 14% for 2.5 and 5 mg of racemic albuterol, respectively."

We also note that one study¹² listed in the draft policy was conducted in an urban tertiary children's hospital to determine whether levalbuterol resulted in fewer hospital admissions than racemic albuterol when used for the treatment of acute asthma. Although clinical trials involving children are not typically considered in making Medicare coverage determinations, it is interesting to point out that the children's study concluded "substituting levalbuterol for racemic albuterol in the emergency department management of acute asthma significantly reduced the number of hospitalizations;" (36% in the levalbuterol group compared to 45% in the albuterol group, P=.02)¹³ Another study on the low-dose effect of levalbuterol (LEV) in children with asthma compared with placebo and racemic albuterol (RAC), which was not cited in the draft policy, concluded that levalbuterol "was clinically comparable to 4- to 8-fold higher doses of RAC, and it demonstrated a more favorable safety profile." According to the study, "LEV 0.31 mg should be used as the starting dose in 4-11 year old children with mild to moderate persistent asthma. Patients with severe disease might benefit from higher doses."¹⁴

It appears that the DME PSCs are basing the determination that the medical necessity of levalbuterol compared to albuterol has not been demonstrated on two recent studies noted in the draft policy. One study conducted by Datta, et al¹⁵ evaluated nebulized levalbuterol in stable COPD involving only 30 patients. Although albuterol has been studied in asthma, the study points out that the "potential usefulness of this short-acting bronchodilator in COPD has received little attention." The study compared the bronchodilator effect and side effects of single doses of nebulized levalbuterol with racemic albuterol alone and combined racemic albuterol and ipratropium. It concluded "for single-dose, as-needed use in COPD, there appears to be no advantage in using levalbuterol over conventional nebulized bronchodilators." The study did note, "levalbuterol resulted in significant bronchodilation compared to placebo at .05 and 1 h following nebulization", but concluded that the results "were not significantly different from that of the other protocols." According to the authors, the "limitation of this study is the relatively

small number of patients studied, thereby reducing its power for statistical inference." It calls for further study testing multiple doses of beta-agonists administered on a regular basis to evaluate the "potential negative effect of accumulation of the S-isomer."

The second study in question, conducted by Lotvall, et al,¹⁶ compared the bronchodilating and systemic effects of R- and RS-albuterol by using a crossover study design involving only 20 asthmatic patients. They concluded that the "R-albuterol/RSalbuterol potency ratios for local (FEV1) and systemic effects (heart rate and K +) are similar, suggesting a comparable therapeutic ratio for R-albuterol and RS-albuterol in asthmatic subjects." An editorial by Ahrens and Weingerger¹⁷ in response to this study, also listed in the draft policy, points out that the findings by Lotvall, et al conflict with those published in other studies. The authors cite "it is appropriate to reexamine the weight of evidence from of all of the published clinical trials that have attempted to test the hypothesized adverse effects of S-albuterol and the associated potential benefits of using levalbuterol rather than racemic albuterol." AARC believes that the DME PSCs have fallen short of this task and are arbitrary in their decision to lower the payment for levalbuterol.

The AARC has recently learned that a new study, which was presented at a meeting of the American College of Chest Physicians in October 2005, has been accepted as a manuscript in the *Journal of COPD* to be published in the fall of 2006. The study assessed the safety and efficacy of levalbuterol in treatment of patients with COPD. It concludes, "Levalbuterol was well tolerated and produced significant bronchodilation and reduced rescue medication use. Racemic albuterol was associated with significantly more study withdrawals due to COPD exacerbations compared with placebo." The general implications are that levalbuterol may offer advantages in the treatment of patients with COPD. An abstract and poster presented at the meeting are attached for your review.

Recommendation

• Withdraw the current draft policy to lower the payment of levalbuterol based on the least costly alternative. Continue to pay for levalbuterol at its 2006 payment allowance and set up screening parameters in place of the draft policy to control the cost and utilization of this effective therapy.

Given the reports and history of albuterol, it appears that the DME PSCs are attempting to ensure that levalbuterol does not become a substitute for that inhalation drug now that the price of albuterol has been significantly reduced. However, the basis for lowering the price of levalbuterol due to lack of medical necessity is clearly unfounded.

The current literature on therapeutic equivalency more than adequately supports the fact that levalbuterol has significant therapeutic value, especially in asthma patients. Also, a soon-to-be published article in *CHEST* further demonstrates the medical necessity of levalbuterol. Since there is insufficient literature, however, with respect to the comparative benefits of levalbuterol versus albuterol in patients with COPD, the DME PSCs should postpone any changes to its current nebulizer policy until additional scientific studies on COPD patients are completed and definitive conclusions can be drawn about the comparative benefits of one over the other.

Therefore, the AARC strongly recommends that the DME PSCs pay for levalbuterol at its 2006 payment allowance and monitor the cost and utilization through its ability to establish screening parameters. This technique has been used effectively to guard against over utilization throughout the program's history, and is by far the more appropriate approach to controlling cost and utilization than using the least costly alternative mechanism.

2. If the DME PSCs go forward with finalizing the draft policy as written, it may severely limit Medicare beneficiaries' access to levalbuterol and have an adverse affect on their ability to receive the medication prescribed by their physicians.

The AARC is particularly concerned that a change in policy could limit access to those patients who actually do benefit from levalbuterol versus albuterol. While patients with asthma and COPD are likely prescribed levalbuterol first in the hospital setting, physicians usually continue the patient's prescription for levalbuterol rather than switching to albuterol since the patients have responded positively to the drug.

The DME PSCs are proposing to base the payment for levalbuterol (J7612 or J7614) on the least costly medically appropriate alternative; that is, payment will be based on the allowance established for albuterol, J7611 and J7613 respectively. As noted above, the decision to make this change in payment is based on the assertion that published, scientific literature indicate there are no therapeutic advantages of levalbuterol over albuterol.

As discussed above, there is sufficient scientific literature to support the medical necessity of levalbuterol versus albuterol. Further, the AARC is aware that there are patient-specific cases where levalbuterol has a better health outcome for that particular patient than albuterol. For example, a COPD patient with a strong cardiac response to beta-agonists experiences symptomatic tachycardia following treatments with racemic albuterol. This same patient can tolerate with minimal cardiac effect the lower dose and single isomer levalbuterol and therefore can remain compliant to therapy in the home.

While we recognize that the proposed change in policy to pay at a lower cost for levalbuterol does not, in theory, restrict a physician from prescribing what he or she believes is the most effective medicine for a particular patient, the AARC wants to go on record in expressing our concern that pharmacies may not continue to stock levalbuterol because the allowance for the drug will be significantly lower, and the pharmacies will no longer be able to afford to continue to make levalbuterol available to its Medicare beneficiaries. Further, we are also concerned that Medicare beneficiaries may be required to pay out-of-pocket the difference between levalbuterol and albuterol via an "Advance Beneficiary Notice."

Recommendation

1. Establish specific criteria under which levalbuterol will be reimbursed at its 2006 established payment allowance.

Based on the experience of respiratory therapists who routinely treat patients with severe pulmonary diseases, the AARC would be happy to work with the DME PACs, as well as other stakeholders, to come up with a set of criteria that would offer limited situations in which levalbuterol could be reimbursed at its current 2006 payment allowance.

As noted in our comments above, the scientific literature supports the medical necessity of levalbuterol. Further, we are aware of situations where patients do better with levalbuterol than albuterol while in the hospital and continue with the levalbuterol treatment in the home after being discharged. If the DME PSCs decide to go forward with a new nebulizer policy without additional research and review of scientific literature, then at a minimum, we recommend that the DME PACs revise their draft policies to take into account those

situations in which levalbuterol is an effective treatment therapy and reimburse levalbuterol at its established 2006 payment allowance.

Recommendation

2. Should the DME PSCs finalize its current draft nebulizer policies without substantive revisions despite oppositions that may be raised through public comments, the AARC strongly recommends that the impact of the decision be studied closely to determine whether lowering the payment allowance for levalbuterol adversely impacts access to this vital drug for those Medicare beneficiaries who clearly need it and benefit from it.

Based on public comment, if the DME PACs finalize their proposed nebulizer policies without substantive changes, the AARC recommends that they study the effects of the pricing methodology on patient access to determine if it adversely impacts the ability of Medicare beneficiaries to purchase the medications they need as prescribed by their physicians. A period of time should be established for the study, and revisions to the nebulizer policy should be made to pay adequately for levalbuterol, if lowering the payment has a deleterious affect of patient access.

Elimination of Coverage of Certain Nebulizer Drugs

1. The proposed change in policy to eliminate coverage altogether for certain nebulized drugs virtually eliminates a physician's ability to prescribe these drugs for any off-label use.

Although some of the drugs proposed to be eliminated now come in the form of metered dose inhalers (MDIs) and dry powered inhalers (DPI), many of the drugs were not originally intended for aerosolized use. Thus, when used in this form, they were considered "off label." The absence of published science in regard to the drugs proposed by the DME PSCs to be eliminated from Medicare coverage does not equate to an absence of medical necessity when prescribed by a physician for a defined application.

Physicians frequently prescribe drugs off label, and through the years, Medicare has evaluated on a case-by-case basis the medical necessity of such use, taking into account generally accepted medical practice. Many off label applications are based on a specific patient condition and response to a unique drug or class of drugs. Rarely is there an abundance of published data to support the particular application with a particular patient. In fact, the AARC would argue that if manufacturers went to the expense to study the effects of off-label use, they would arguably ask the Food and Drug Administration, based on its findings, to approve new indications for use of a particular drug and revise its labeling.

Recommendation

• The DME PSCs should reconsider their proposed policy to summarily dismiss certain nebulizer drugs from coverage and its affect on the ability of physicians to prescribe off-label uses for their patients that over time have become generally accepted medical practice.

The AARC is extremely concerned that the non-coverage decision for these drugs completely eliminates the ability of a physician to prescribe these drugs for a Medicare patient under the Part B benefit because the drugs would no longer be covered. In such cases, the patients would be required to pay out-of-pocket. Further, now that MDIs and DPIs will be covered under Medicare Part D, we are concerned that the impact of this non-coverage decision could carry over into Part D and that none of these drugs will be covered by either program.

Summary

If the intent of the proposed change to reduce the payment of levalbuterol is to control utilization and cost, then the AARC recommends the DME PSCs establish screening guidelines to monitor utilization rather than reduce the payment amount for levalbuterol, which effectively will eliminate its availability to Medicare patients who benefit from this treatment over albuterol.

There is more than sufficient scientific literature to support the conclusion that levalbuterol has specific advantages over albuterol in a number of situations and, indeed, meets the test of medical necessity. The decision to lower the payment allowance for levalbuterol to that of albuterol because the medical necessity of levalbuterol has not been established is unfounded and arbitrary.

To go forward with the proposed policy as drafted will seriously impact Medicare beneficiaries' access to their prescribed medications and can have a detrimental effect on health outcomes. If the DME PSCs go forward with changes to its current nebulzier policy, then the policy change should be to establish specific criteria under which levalbuterol will be reimbursed at its established payment allowance where its benefit has been demonstrated in clinical studies.

To summarily non-cover certain nebulized drugs because there is no evidence to support their use effectively eliminates a physician's ability to prescribe a medication for "off label" use. Medicare has traditionally reviewed off label use on a case-by-case basis, and should continue to do so with respect to the drugs it proposes to eliminate from coverage.

Thank you for considering our comments in this matter. We hope that the DME PSCs will take our recommendations into consideration and postpone issuing a final decision until further evaluations are undertaken.

Sincerely,

Michael W. Runge, RRT
President-2006

Spencer, Francina C. (CMS/OCSQ)

From: CMS CAGInquiries
Sent: Wednesday, January 24, 2007 117 PM
To: Spencer, Francina C. (CMS/OCSQ)
Subject: FW: PUBLIC COMMENT Title of NCNCAL Nebulized Beta Adrenergic Agonist Therapy for Lung Diseases
Importance: High

On 1/19/07, I submitted a comment (pasted below) on the CMS Coverage website re above titled NCA, and got the error message pasted below. I am pasting my comment below so that it might be received in a timely manner.

ERROR MESSAGE:

>Microsoft VBScript runtime error
>ActiveX component can't create object
'CDONTS.Newmail/mcd/public_comment_response.asp., line 37

>PUBLIC COMMENT

>

>RE: NCA: Nebulized Beta Adrenergic Agonist Therapy for Lung Diseases

>

>1/19/07

>

>To whom it may concern:

>

>Below, I make four comments or request for clarifications.

>First, I suggest the comment period for this NCA be extended, given that this NCA was removed or not available on the website for some indeterminate period of time earlier this week. Moreover, I recommend CMS send an e-mail notification to that effect on an appropriate CMS LISTSERV.

>Second, I request a clarification of the scope of this National Coverage Analysis (NCA). The NCA states, "CMS has internally generated a formal request for a National Coverage Analysis to determine when treatment with a nebulized beta adrenergic is reasonable and necessary for Medicare beneficiaries with COPD". That statement implies review of all beta agonists, both short and long lasting. However, the NCA text emphasizes an interest in nebulized levalbuterol, which may lead some potential commentators to limit the scope of their comments.

>Indeed, the broader scope would be appropriate given the conclusion of a draft (and still pending) Nebulizer Policy published by the three DME Program Safeguard Contractors (PSCs) on March 24, 2006. That draft proposes to eliminate coverage for bitolterol, formoterol, and terbutaline "because there is inadequate support in the medical literature for administration using a DME nebulizer".

>By way of background, short-acting beta agonists include salbutamol (albuterol), levalbuterol, terbutaline, pirbuterol, procaterol, metaproterenol, fenoterol, bitolterol mesylate. Long-acting beta agonists include salmeterol, formoterol, and bambuterol. And, in October 2006, the FDA approved arformoterol (proprietary name: Brovana).

Third, I request a clarification of the statement “CMS has become aware of concerns regarding the appropriate use of nebulized beta adrenergic agonist therapy for lung diseases.” Could CMS provide some discussion of the concerns?”

Fourth, I request a clarification if CMS could, under the CMS policy governing National Coverage Analyses (NCA) and National Coverage Determinations (NCD), endorse or establish claims for a drug product that have not been approved by the FDA, or, moreover, actually prohibited by the FDA.

For example, Xopenex (levalbuterol HCl) inhalation Solution was approved by the Food and Drug Administration (FDA) on March 25, 1999. Although the FDA concluded that Xopenex was “safe and effective” per the approved label (see FDA Approval Package, link below), the FDA subsequently warned the manufacturer of Xopenex, Sepracor, Inc., of Marlborough, MA, on two separate occasions, to “cease immediately” making certain claims that Xopenex was safer or more effective than racemic albuterol (see links below). To my knowledge (a fact question that should be independently ascertained), the FDA has not subsequently approved any claims of superior safety or efficacy for Xopenex. (For a completed record, it would also be useful to know if Sepracor has requested FDA approval of additional safety or efficacy claims, and on what basis; or if Sepracor has funded or encourage such studies, published or unpublished. I suggest Sepracor be directly asked by CMS if the company has any such additional data.)

LINKS:

FDA – Approval Package – Xopenex (Levalbuterol HCl) Inhalation Solution; Company: Sepracor Inc. (Application No. : 20837) (Approval Date: 3/25/1999)

LINK: http://www.fda.gov/cder/foi/nda/99/20837_Xenopex_approv.pdf

FDA – Warning Letter to Sepracor re Xopenex Marketing Claims (3/26/99)

LINK: www.fda.gov/cder/warn/mar99/032699_sepracor.pdf

FDA – Warning Letter to Sepracor re Xopenex Marketing Claims (5/21/99)

<http://www.fda.gov/cder/warn/may99/7961.pdf>

Thank you for the opportunity to comment on this matter.

R. Alexander Vachon, III, Ph.D.
Hamilton PPB
2100 Connecticut Avenue, N.W.
Suite 208
Washington, D.C. 20008

Spencer, Francina C. (CMS/OCSQ)
From: CMS CAGInquiries
Sent: Wednesday, January 24, 2007 1: 15 PM
To: Spencer, Francina C. (CMS/OCSQ)
Subject: FW: NCA for Nebulized Beta Adrenergic Agonist Therapy for Lung Diseases (CAG-00354N)

From: Miriam O'Day [mailto:moday@alphaone.org]
Sent: Friday, January 19, 2007 5:25 PM
To: CMS CAGInquiries
Subject: NCA for Nebulized Beta Adrenergic Agonist Therapy for Lung Diseases (CAG-00354N)

Alpha-1 Foundation.
2937 SW 27th Avenue, Suite 302
Miami FL, 33133

The COPD Foundation, Inc
2937 SW 27th Ave., Suite 302
Miami, FL. 33133

VIA E-MAIL

January 19, 2007

Tiffany Sanders, MD
Francina Spencer
Coverage and Analysis Group. Office of Clinical Standards and Quality
Centers for Medicare and Medicaid Services
Mail Stop C1-09-06
Baltimore. MD 21244

RE: NCA for Nebulized Beta Adrenergic Agonist Therapy for Lung Diseases (CAG-00354N)

Dear Dr. Sanders and Ms. Spencer:

These comments are submitted on behalf of the Alpha-I Foundation and COPD Foundation. The Alpha-I Foundation is dedicated to providing leadership and resources that will result in increased research, improved health, worldwide detection and a cure for Alpha-I. The COPD Foundation was founded to provide a variety of services and support to persons who are affected by Chronic Obstructive Pulmonary Disease (COPD), whether they are sufferers, care givers, health professionals, or family and friends, through research, education, and increasing public awareness including the need for early screening and diagnosis.

Alpha-1 is a devastating disorder, a pediatric liver disease that requires transplantation and an adult onset degenerative lung disease that leads to repeated infections and progressive loss of lung function. The median age of survival for Alpha-1 is 54. The most common signs and symptoms of Alpha-1 are recurring respiratory infections, shortness of breath or awareness of one's breathing, non-responsive asthma or year-round allergies, rapid deterioration of lung function without a history of significant smoking, decreased exercise tolerance, chronic liver problems, and elevated liver enzymes.

Chronic obstructive pulmonary disease (COPD), also known as chronic obstructive lung disease (COLD), is an umbrella term used to describe anyone or all of a group of progressive lung diseases, encompassing emphysema, chronic bronchitis, refractory asthma, and severe bronchiectasis. This progressive disease is characterized by increasing breathlessness and shortness of breath. It is the 4th leading cause of death, and projected to be the third leading cause by 2020. COPD is an insidious disease, which is often first diagnosed after some of the lung capacity is already lost. It is possible to have COPD without knowing it, however, the diagnosis is easily made by measuring the pulmonary function. An early diagnosis is important, as once the lung capacity is lost, it cannot be regained.

Individuals suffering with Alpha-1 and COPD require access to life-saving therapy and cannot be subject to fluctuations in benefits that may disrupt their health. We are expressing concern about the inconsistency in the NCA language which may unintentionally limit patient access to care. Treatment of COPD and Alpha-1 includes the use of both MDI and nebulized medications. And while we are aware that data may show MDI as a preferred administration, particularly in the home many COPD patients have difficulty with MDI administration. This is for various reasons including that they may be physically unable to operate the device due to arthritis or may have compliance problems due to lack of education and misunderstanding. In a soon to be published co-morbidity study of 3,000 COPD patients in New York, 30- 40% of these patients use a daily nebulizer. This may be favorable because of physical administration issues, and also because in COPD the moisturization and humidity may deliver medication better than dry powder in an MDI. We bring these matters to your attention because the consequences of policy change may not be fully understood because of ambiguous language in the NCA. On behalf of COPD patients we urge CMS to review your process so as not to cause unintentional damage to our community.

The COPD Foundation and the Alpha-1 community requests that CMS carefully review the recommendations received and extend the comment period for an additional 30 days to allow greater clarification of the NCA.

Sincerely,

Miriam O'Oay
Senior Director Public Policy

Miriam Q'Day
Senior Director Public Policy
Alpha-1 Association
Alpha-1 Foundation



AMERICAN ASSOCIATION FOR RESPIRATORY CARE
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(972) 243-2272, Fax (972) 484-2720
<http://www.aarc.org> E-mail: info@aarc.org

December 30, 2006

Ms. Francina Spencer
Centers for Medicare and Medicaid Services
OCSQ/CAG/DID
Mail Stop C1-09-06
7500 Security Boulevard
Baltimore, MD 21244

RE: Nebulized Beta Adrenergic Agonist Therapy for Lung Diseases (CAG-00354N)

Dear Ms. Spencer:

The American Association for Respiratory Care (AARC) is responding to the request for public comment on the NCA Tracking Sheet for Nebulized Beta Adrenergic Agonist Therapy for Lung Disease.

In May of this year the AARC, an association representing over 42,000 respiratory therapists submitted comments to the proposed revisions to the Durable Medical Equipment Program Safeguard Contractors' (DME PSCs) local coverage determination concerning nebulizers. As part of the comments we enumerated the findings of numerous studies and reviews regarding the efficacy and clinical differences between albuterol and levalbuterol.

We have attached these comments for your consideration as you deliberate a coverage determination. The discussion of the clinical studies begins on page 2 under "Payment for Levalbuterol" and continues through page 5.

The AARC supports the Centers for Medicare and Medicaid Services development of a coverage determination regarding the treatment with nebulized beta adrenergic agonist for the Medicare patient with Chronic Obstructive Pulmonary Disease (COPD).

Sincerely,

A handwritten signature in black ink, appearing to read 'Toni Rodriguez'.

Toni Rodriguez, EdD, RRT
President



January 15, 2007

Francina Spencer
Lead Analyst
DHHS
Baltimore, MD

Dear Ms. Spencer,

I am writing in response to the recent posting by DHHS regarding nebulized beta adrenergic agonists and request for comments. This is an important area of interest for us as well as important for patients with COPD.

Use of inhaled aerosols has revolutionized the care of patients who have been diagnosed with asthma and COPD by allowing the selective delivery of optimal concentrations of drugs to the airways while minimizing the undesirable side effects that result from systemic administration. Beginning with early beta2-agonists, inhaled Isoproterenol demonstrated a clear benefit to these patients. This drug was followed by inhaled Albuterol sulfate, which provided a longer acting response of at least four hours.

Today, Albuterol is still a workhorse product for the treatment of asthma and COPD. Albuterol however is not without its detractions. When the drug is absorbed into the pulmonary circulation, undesirable side effects including palpitations, tremors, and nervousness have been reported in some patients. For this reason, a newer isomer formulation (Levalbuterol) of Albuterol sulfate was introduced and is commercially sold as Xopenex. Levalbuterol is potentially an even longer acting beta2-agonist, perhaps providing bronchodilation up to 8 hours and with a reduction in side effects. The cost of Xopenex however is two to seven times the cost of Albuterol and is therefore outside the reach of many patients with asthma or COPD, both diseases with high prevalence in the poorer socioeconomic populations.

The side effects of Albuterol are directly related to the dose delivered and absorbed into the blood stream. There is also compelling data that depending on how aerosols are delivered to the airways, that one could control how much drug is delivered to the smooth muscle and beta2 receptors, how much is deposited and absorbed in the oropharyngeal/gastric regions, and how much would be deposited into the alveoli. Defining where an aerosol is deposited, can therefore determine the magnitude of the side effects. We hypothesized that rather than using a pharmacologic approach to reducing side effects (as done with Levalbuterol), we might be able to attain the same benefit with a less expensive technological approach to deliver Albuterol.

Delivery and deposition of aerosols are determined by both the aerosol characteristics and by the patient's breathing characteristics.

The aerosol characteristics include:

- Particle size
- Hygroscopicity
- Particle shape
- Geometric standard deviation of the aerosol cloud
- Timing of an aerosol bolus

The patient's breathing characteristics include:

- Inhaled volume of air
- Inspiratory flow rate
- Breath holding

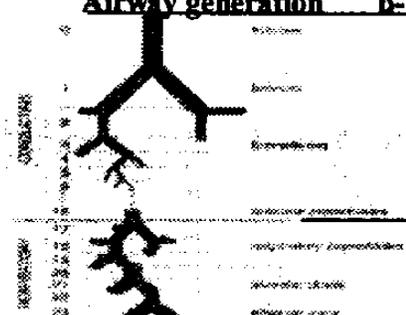
If one can control the aerosol as well as the patient breathing characteristics, one can control deposition. The ability to select particle size and deliver a timed monodispersion aerosol while controlling the patient's breathing characteristics creates uncharted capabilities, however tremendous clinical potential.

The beta2 receptors in the lungs (responsible for smooth airway tone) are most heavily concentrated in the 20 - 23rd generations of the airways, however, the greatest number of receptors located where the greatest mass of airway smooth muscle is found, is along the 3rd and 4th through the 12th generation. Therefore, the large conducting airways from approximately the 3rd generation down to the terminal bronchioles are capable of responding to beta agonists. To maximize the therapeutic response and reduce airway constriction, specific segments of this entire region of the airway should be treated; something that does not occur with existing nebulizers or MDI products.

Discussion

- **Airway smooth muscle (ASM) distribution & Bronchodilation**

Airway generation	β-receptor density	ASM mass
Trachea	*	**
Bronchi	**	****
Terminal bronchioles	*****	*



- **Local airway mucosal drug concentration**
Airway surface area ↑ exponentially; [conducting] >> [alveolar]
- **Hygroscopic growth**
In vitro models - but sparse *in vivo* data; ?growth a misnomer
- **Blood flow redistribution**

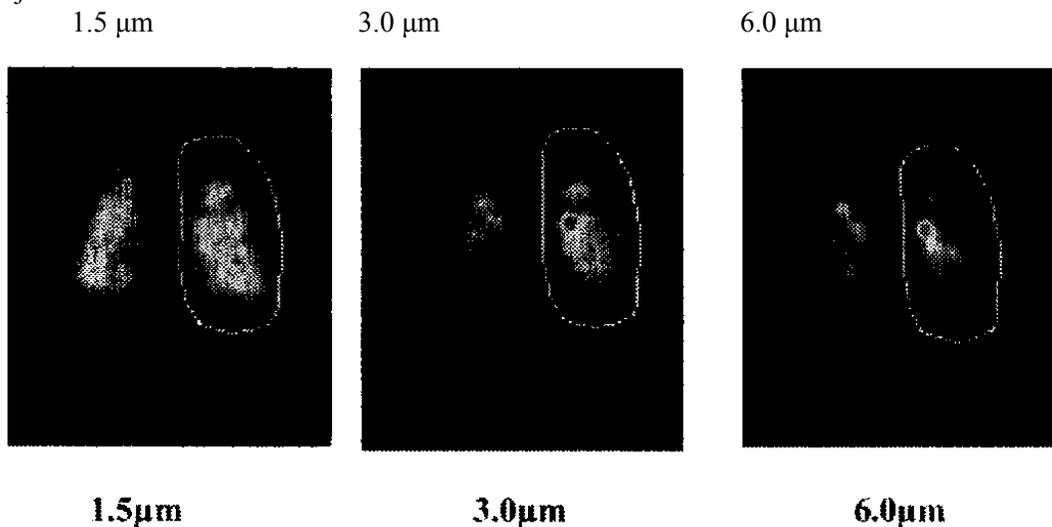
If one can control the particle size and forward velocity of the aerosol cloud generated, one can determine what generation of airways the particle will be deposited in. The particle size (as demonstrated by independent investigators) that may produce the greatest change in FEV1 is

suggested to be 6 micrometer. (Usmani) An isokinetic aerosol of this size deposits predominantly in the more central airways, minimizing peripheral deposition in the alveoli, where there may be less therapeutic benefit, but significant systemic absorption occurs. This finding is in contrast to the clinical literature with conventional nebulizers and MDI's, as these latter delivery devices have significant aerosol velocities and very wide particle size distributions. Additionally, none of these devices are able to control the breathing pattern of the patient and different breathing patterns can produce differences in lung deposition by as much as a factor of five-fold (Brand et al. 2000). Therefore, total deposited doses and regional deposition vary widely between patients using these devices, making it difficult to isolate pharmacologic effects with particle size or dose. Clinical variations are managed by prescribing a wide range of doses and blanket coverage within the respiratory tract, often leading to adverse side effects.

A panel of gamma scintigraphy images below illustrates that as the particle size increases in a well controlled aerosol, more particles (drug substance) are focused within the conducting airways where the smooth muscle target is located. There is also significantly less drug deposited in the peripheral alveolar spaces of the lung, where there is no smooth muscle, but where drug is readily absorbed into the blood stream, and may cause unwanted effects on distal organs.

Regional Deposition Images

Gamma camera images of ^{99m}Tc -labelled monodisperse albuterol aerosols in the same asthmatic subject



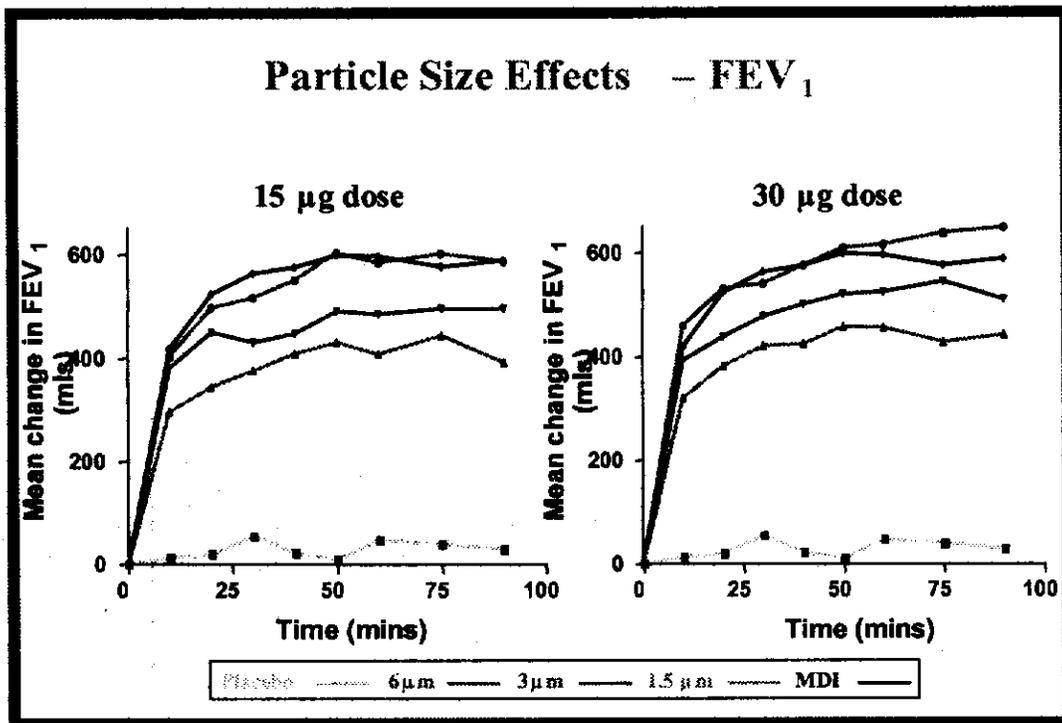
The physiologic questions are slightly more complex. Few commercial devices can effectively deliver a whole dose of 6-micron particles to the lungs with a high fraction of the aerosol within the respirable range to test this hypothesis. Alternatively, with breath flow control and bolus timing control, it is possible to deliver smaller sized particles, while limiting their deposition to these same airways.

Inhaled Albuterol preparations contain "labeled indications" that the effect will last for 4-6 hours. Most devices nebulizing Albuterol deliver a broader spectrum of particles sizes that cover a wide range of airway generations as well as cause a significant portion of the drug to be impacted in the oropharynx and swallowed or directly absorbed. Therefore, most delivery systems potentially can have different durations of effect modified by several mechanisms. These mechanisms may

include direct deposition on the beta2 receptors, recirculating gastrointestinally absorbed Albuterol by the blood to the receptors and movement of distally deposited Albuterol to the receptors by the mucocilliary transport system.

The pharmacologic effects of Albuterol are at least in part attributable to stimulation through beta-adrenergic receptors of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'adenosine monophosphate (cyclic AMP). Increases cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially mast cells.

Duration of effect by drug deposition on the receptor site has been studied by Williams, et al, who reported that loss of agonist coupling for Albuterol to be 14.8% per hour. Usmani's study reported that a half dose (15 µgram) of Albuterol was nearly effective as 30 µgrams and the effect was measured out to 100 minutes. This study used laboratory based research particle production devices that selected and controlled particle size and velocity of delivered aerosols.



This data would suggest that direct deposit of only 30 µgrams of 6-micron particles of Albuterol directly to the receptors might have an effective duration effect of at least 5 hours.

Swallowed Albuterol from conventional nebulization of 3 mg of Albuterol (typical adult dose is 2.5 mg) has been studied in adults. These reports indicate that blood levels from gastric absorption at 0.5 hours were 2.1 ng/ml (range, 1.4 - 3.2 ng/ml). In comparison, blood levels following a therapeutic oral dose of Albuterol of 2 to 4 mg are about 10 times greater (-18 ng/mL), with similar clearance rates and half-lives. These high blood levels following oral dosing are required to effect a beta receptor response in the airways, but also have profound receptor responses on other smooth muscle tissue in the body, most notably cardiac and vascular smooth muscle and intestinal smooth muscle. These responses lead to increased heart rate and blood pressure, and intestinal cramping. The significantly lower blood levels from gastric absorption

following inhaled therapy contribute little if at all to the clinical effect on airway tone modulation and therefore probably have no contribution to the duration or magnitude of effect.

Movement of Albuterol up the mucociliary bed and re-stimulation of the receptors is an unlikely effect of peripherally deposited particles. Albuterol is a rapidly absorbed product and therefore little would be expected to remain on the airway surface for transport to the 3rd and 4th generation of airways, particularly with the greatest concentration of receptor sites located in the distal regions of the airways. Additional support of this theory comes from Usmani's data that demonstrated that 1.5 micron particles had a lower effect on FEV₁ and its effect began diminishing at 60 minutes, in contrast to the increasing effect of the 6 micron particles, even out to 100 minutes.

The data supports the theory that if a high dose of Albuterol can be deposited in the larger airway generations and prevented from entering the pulmonary circulation from the lung periphery, that the largest magnitude of bronchodilator response may be attained with the lowest circulatory absorbance. Based on this data and in consideration of the deposition variation that would be anticipated in Clinical use, a targeted deposition of 45 µg was selected for our studies. We expect that this would provide for a sustained response without the undesirable side effects.

To control the aerosol characteristics for our study, an Activaero APIXNEB system, based on the Pari eFlow nebulizer was used for the investigational strategies. The APIXNEB system is built around a small vibrating disk that has 4,000 laser precision drilled holes in it. The disk is vibrated on the surface of the Albuterol at more than 100,000 times per second. This pulls the liquid through the holes to form droplets of precise uniform size. This method produces very little forward velocity. It has many significant benefits over conventional nebulizers including:

- > 90% respirable fraction (high mass transfer)
- Selection of hole size can adjust particle size (targeted deposition)
- Near isokinetic aerosol (zero velocity assures low oral impaction and swallowing)
- High precision dose delivery (± 5%)
- Geometric standard diameter (GSD) -1.51 (near mono-dispersal bandwidth)
- Requires no special formulation for Albuterol

To control the patient's breathing characteristics for this protocol an Akita² Delivery System developed by Activaero GmbH was used. The Akita² uses an integrated eFlow to control how the Albuterol will be deposited and can be programmed with a specific breathing pattern for each patient. The Akita² senses the beginning of subject's inspiration and then flows filtered air into the subject's lungs at a controlled flow rate. At the programmed inspired volume for nebulization, the eFlow is energized (activated) to produce a specific bolus of Albuterol and it is flowed into the airways of the subject, followed by filtered air for a volume to clear the upper airway and limit oropharyngeal deposition. The subject can then exhale. By selection of different eFlow hole sizes, the aerosol size is controlled and by selection of the timing of the nebulization and inspiratory flow rate, the deposition is controlled. The loading dose in the nebulizer can then be calculated to deposit the 45 µg at the desired airway branching level.

Modeling of aerosol deposition using computer based programs were used to determine how different particle sizes, using the different nebulizers for our study and different timing of bolus delivery and breathing patterns, would affect deposition.⁷⁻¹⁰ To verify the effects of central versus peripheral deposition, two different particle sizes and two different deposition sites were selected and the models run to calculate the loading dose required to deposit 45 µg in the 3rd - 16th generations or 45 µg in the 17th - 25th generations of the airways. The following four figures are

the results from the model for the standard Pari jet nebulization, and the three models using 6 micron and 3.5 micron particles selected for our study.

Standard Pari Nebulizer:

Nebulizing 2.5 mg (loading dose) will deposit 140 µg in generations 1-16 and 131.3 µg in generations 17-25. This calculation was done for a mean breathing pattern and is subject to high inter- and intrasubject variability.

6 Micron particles with a late bolus delivery:

Nebulizing 112 µg (loading dose) will deposit 45 µg in generations 1-16 and only 4.7 µg in generations 17-25 with the Akita²

3.5 Micron particles with late bolus delivery:

Nebulizing 188 µg (loading dose) will deposit 45 µg in generations 1-16 and 12.3 µg in generations 17-25 with the Akita²

3.5 Micron particles with early bolus delivery:

Nebulizing 98 µg (loading dose) will deposit 23.9 µg in generations 1-16 and 45 µg in generations 17-25 with the Akita²

The modeling suggested that we can clearly separate the deposition and therefore the beneficial and adverse effects of Albuterol based on where the drug is delivered and thereby identify whether it is possible to improve the use of Albuterol for asthmatic and COPD patients. In all of the three Akita² modes, we deliver significantly less drug to the airways.

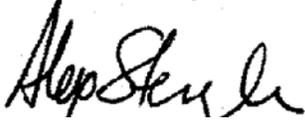
We are in the middle of a study taking place in Toronto, Canada under the guidance of Noe Zamel, MD, a world-renown investigator in the area of chronic airway obstruction, to explore whether a less expensive technical approach can match the pharmacologic performance attributed to Levalbuterol. This first phase study is comparing 2.5 mg (2500 µg) of Albuterol delivered with a standard Pari jet nebulizer with the three investigational low doses of 98 µg, 112 µg, and 188 µg at two different particle sizes and deposition patterns delivered with the Akita²

At this point in the study, as demonstrated by the following four graphs, we have found that all of the lower doses can improve FEV1 by at least 20% and the 188 µg dose delivered to the central airways provided equivalent bronchodilation and equivalent duration as the standard inhalation of 2.5 mg of Albuterol. Of significance, there was a total elimination of the heart rate stimulation that was observed with the standard delivery as well as elimination of the tremor as measured by finger accelerometer, associated with this drug.

We believe that our studies demonstrate that by taking advantage of these technologic features, patients with COPD will benefit by needing only 1/14th the standard nebulized dose of Albuterol to attain the same airway response as measured by FEV1. We believe that the reduced dose significantly lowers the side effects associated with standard treatments while providing similar and more targeted doses to the site of disease and at the same time enables use of less expensive drugs for their treatment. We anticipate that the increased cost of the technology to attain these benefits will be far lower than the cost for six-months of more expensive Levalbuterol formulations and may preclude the need for its use if the only benefit sought is reduced side effects. We are nearing completion of the required studies for device submission and anticipate that this technology will be commercially available in the US by the end of this year.

I hope that this data and information is useful to the Department of Health and Human Services in determining how best to assist patients with chronic obstruction pulmonary diseases. If you have any questions or require additional information, please do not hesitate to contact me.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Alex Stenzler". The signature is written in a cursive style with a large initial "A" and a long, sweeping underline.

Alex Stenzler
Vice President
Advanced Technologies

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January 17, 2007

The Centers for Medicare and Medicaid Services
<http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=198>

Dear Sirs;

I am very concerned with the decisions about to be made concerning the appropriate coverage for Xopenex for those Medicare beneficiaries who suffer from COPD, especially the medical necessity of Xopenex UDV and nebulizer therapy.

In 1999, we began using Xopenex hy nebulizer in patients suffering from bronchospasms in our COPD and Asthma patients. This not only provides bronchodilator effects but also provides hydration to the airways, which encourages expectoration of mucous when needed to clear the airways.

We have continued to use Xopenex IJDV as our bronchodilator for the following reasons:

1. Xopenex UDV is only given Q8 hours (7am, 3pm & 11 pm) - in a year long study we conducted in 2005 we found that patients ordered Q8 hours with a PRN order of Q3 hours very seldom called for extra treatments. 1 out of 10 patients may need an extra treatment within a 24 hour period. We also found that patients had a shorter length of stay when in the hospital than before with the use of racemic albuterol, and had fewer readmissions within a 30-day period.
2. Patients experienced less restlessness and nervous feelings when using Xopenex and are found to sleep through the night. When using racemic albuterol patients needed treatments all through the night (this interfered with their sleep). Being able to sleep through the night and be more rested helps to increase the patient's ability to function and perform daily life activities better.
3. Patients who have a choice of nebulized short-acting beta agonists have all chosen to use nebulized Xopenex, their reasons are one & two above.
4. It is very important for patients to have the choice of using Xopenex UDV and to be able to remain on this product even after the coverage restrictions are in place. If patients are not allowed to use Xopenex they will not receive the longer action of the bronchodilator and will have to have treatments more frequently with will decrease their rest time, their freedom from having to take treatments every 3-4 hours and this will decrease their quality of life.

There is a lot of different published research both clinical and pre-clinical that supports our decision to use Xopenex for the treatment of COPD. Our biggest reason for the continued use of Xopenex is the outcomes seen in our patients.

Published data:

Inpatient Use of Bronchodilator Nebulizer Treatments with Levalbuterol and Albuterol:
A Cost-Effectiveness Analysis. Vickie Ganey, MBA, RRT, RPFT, RN, LNC Manager
Cardiopulmonary Services. Halifax Regional Hospital, South Boston. VA AARC poster
presentation 2006