Budesonide Literature Review
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FOOD AND DRUG ADMINISTRATION (FDA) INFORMATION
The FDA requires manufacturers of pharmaceutical products and medical devices to indicate on the package label the uses of the product. For drugs and biologicals, this information is based upon clinical studies typically published in peer-reviewed medical journals. At the time of drug approval, the FDA also dictates to the manufacturer the exact use(s), patient population(s) and dosages that may be included in the instructions/package insert to healthcare providers and patient. This information is commonly called the “label” for the drug and may not be changed by the manufacturer without prior FDA approval. Furthermore, pharmaceutical manufacturers are not allowed to market or otherwise publicize their drug for diagnoses, dosages, patient populations or routes of administration other than what is listed in the FDA-approved label.

The FDA-approved form of budesonide for inhalation via nebulized solution is Pulmicort Respules® (AstraZeneca LP). Pulmicort Respules® are provided in unit dose containers in 0.25 mg, 0.5 mg and 1.0 mg dosages and have a labeled indication for asthmatic patients 12 months to 8 years of age. There is no labeled indication for use in adults or for other diagnoses such as chronic obstructive pulmonary disease (COPD), bronchiectasis, bronchitis or emphysema. Consequently, its use in adult populations or for asthma and other pulmonary diseases is considered an “off-label” indication.

CENTERS FOR MEDICARE & MEDICAID SERVICES REGULATIONS
The Centers for Medicare & Medicaid Services (CMS) has issued to contractors instructions for the coverage of medications for off-label indications in the Medicare Internet-Only Benefits Manual 100-2, Chapter 50. According to CMS, FDA approved drugs used for indications other than what is listed on the official label may be covered under Medicare if the carrier determines the use to be medically accepted, taking into consideration the major drug compendia, authoritative medical literature and/or accepted standards of medical practice. The manual further cites situations where off-label use is considered “not medically necessary” in Chapter 50.4.3. This section specifically addresses excessive medications stating:

Medications administered for treatment of a disease and which exceed the frequency or duration of injections indicated by accepted standards of medical practice are not covered.

This section provides additional instructions for how contractors are to handle claims for excessive amounts of medications:

If a medication is determined not to be reasonable and necessary for diagnosis or treatment of an illness or injury according to these guidelines, the carrier excludes the entire charge (i.e., for both the drug and its administration).

Considering the FDA labeling and above guidance from CMS, the use of budesonide (HCPCS code J7626 – Budesonide, inhalation solution, FDA-Approved final product, non-compounded, administered through DME, unit dose form, up to 0.5 mg) in the treatment of adults with asthma and chronic obstructive pulmonary disease (COPD) is considered off-label and its use must be supported by clinical evidence.
CLINICAL EVIDENCE REVIEW

Standards of Practice for the treatment of pulmonary diseases recognize that inhaled corticosteroids are an efficacious treatment strategy. The Global Initiative for Obstructive Lung Disease (GOLD) guidelines are an authoritative source for accepted standards for the treatment of COPD. Published in 2005, the GOLD recommendations were rapidly accepted as a clinical framework and guidance to clinicians for the treatment of chronic lung disease in adults. According to the GOLD report, inhaled glucocorticosteroids are an integral component of pharmacologic therapy in COPD. The following quotes the findings in the GOLD report (page 53).

Inhaled glucocorticosteroids

Regular treatment with inhaled glucocorticosteroids does not modify the long-term decline of FEV1 in patients with COPD. However, regular treatment with inhaled glucocorticosteroids is appropriate for symptomatic COPD patients with an FEV1 < 50% predicted (Stage III: Severe COPD and Stage IV: Very Severe COPD) and repeated exacerbations (for example, 3 in the last 3 years) (Evidence A). This treatment has been shown to reduce the frequency of exacerbations and thus improve health status (Evidence A), and withdrawal from treatment with inhaled glucocorticosteroids can lead to exacerbations in some patients. Re-analysis of pooled data from several longer studies of inhaled glucocorticosteroids in COPD suggests that this treatment reduces all-cause mortality, but this conclusion requires confirmation in prospective studies before leading to a change in current treatment recommendations. An inhaled glucocorticosteroid combined with a long-acting β2-agonist is more effective than the individual components (Evidence A).

The dose-response relationships and long-term safety of inhaled glucocorticosteroids in COPD are not known. Only moderate to high doses have been used in long-term clinical trials. Two studies showed an increased incidence of skin bruising in a small percentage of the COPD patients. One long-term study showed no effect of budesonide on bone density and fracture rate, while another study showed that treatment with triamcinolone acetonide was associated with a decrease in bone density. The efficacy and side effects of inhaled glucocorticosteroids in asthma are dependent on the dose and type of glucocorticosteroid. This pattern can also be expected in COPD and needs documentation in this patient population. Treatment with inhaled glucocorticosteroids can be recommended for patients with more advanced COPD and repeated exacerbations.

The GOLD guidelines and others have established that inhaled glucocorticosteroids are standard of care for patients with advanced COPD; however, it also establishes that the dose-response relationships are not known. This statement is critical to consideration for off-label use of Pulmicort Respules®. To determine the commonly recommended dosage and treatment frequency of budesonide, an extensive literature review on PUBMED using the search terms “budesonide,” “nebulized budesonide,” “inhaled glucocorticosteroids,” “asthma” and “COPD” was conducted. Articles were excluded when the treatment was for pediatric populations and acute exacerbations of COPD. Only English-language articles were reviewed. Abstracts only were excluded. In addition, a request was sent to the manufacturer AstraZeneca to provide clinical literature supporting the use of Pulmicort Respules® in adult, stable COPD patients. AstraZeneca’s response only duplicated the articles from the literature search.

The literature search resulted in no articles describing the use of nebulized budesonide in the long-term treatment of stable COPD. There were five articles describing its use in acute exacerbations and treatment in either an emergency department or hospital setting; however, none described use in the home setting. Moreover, one is unable to compare the studies with respect to dosing frequency and amount due to differing study designs, patient populations and treatment regimens.

The only studies detailing use of budesonide in adult, stable COPD patients involved the use of powder forms of the medication administered via dry powder inhaler (Turbuhaler®, AstraZeneca), not the nebulized form Pulmicort Respules®. Six articles were reviewed and are summarized below.
Leigh, et.al. (2006) examined the role of inhaled corticosteroids in stable COPD. While the purpose of the study was to examine whether sputum eosinophilia predicted clinical benefit from inhaled steroids, the study utilized “high dose” inhaled budesonide via Turbuhaler®. In this study, high dose was 1,600 μg/day (1.6 mg/day).

Masoli, et.al. (2004) conducted a meta-analysis of dose-response relationships for inhaled budesonide in adolescent and adult asthma populations. The meta-analysis examined only placebo-controlled, randomized clinical trials where at least two doses per day of budesonide were delivered either by Turbuhaler® or metered-dose inhaler + spacer. A total of 6 studies met criteria for inclusion in the analysis. The authors concluded that most of the therapeutic benefit of budesonide was achieved with a dose of approximately 400 μg/day (0.4 mg/day) and maximum effect is achieved at 1000 μg/day (1.0 mg/day).

In a “Letter to the Editor” published subsequent to the Masoli article, Ingelf et.al. from AstraZeneca comments that after 20 years, there is still no consensus on exactly which dose to use in an individual asthma patient. However, they also comment that “Most of our experience tells us that no difference in clinical efficacy will be detected, for example, when doubling the dose of inhaled steroids.”

In a review of the treatment of COPD, Calverley (2001) noted that all studies are in agreement in finding no beneficial effect of any of the inhaled steroids (budesonide, fluticasone propionate and triamcinolone) on the rate of decline of FEV1 with time. Calverley goes on to quote the 2001 GOLD guidelines where inhaled corticosteroids in moderate dose (800 μg/day budesonide/100 μg/day fluticasone) are used for patients with FEV1 < 50% predicted and the patient has at least one exacerbation per year.

Reddel, et.al. (2000) attempted to determine if outcomes in poorly controlled asthma patients could be improved by starting with higher doses of inhaled budesonide (by Turbuhaler®) that recommended by international guidelines. The authors compared 3,200 μg/day to 1,600 μg/day and concluded that 1,600 μg/day was sufficient to lead to optimal control in most subjects. This study did not include COPD patients and had few Medicare-age population patients enrolled in the study. In addition, there was no cohort of patients who received amounts less than 1,600 μg/day as in previous studies demonstrating efficacy at lower doses.

Pauwels et.al. (1999) examined the impact of long-term treatment with inhaled budesonide in persons with COPD who continue to smoke. The study included 912 subjects who were randomly assigned to twice-daily treatment with either 400 μg of budesonide or placebo. Patients were followed for three years. The purpose of the study was to evaluate the impact of inhaled steroids on decline in FEV1 and not the optimal dosage of medication; however, it is illustrative of the dosage of inhaled budesonide considered to be efficacious in the treatment of COPD.

**LITERATURE SUMMARY**

Use of inhaled glucocorticosterioids is a well-established treatment option for adult patients with moderate to severe asthma or COPD; however, there is no literature supporting the use of the FDA-approved formulation of budesonide for nebulized inhalation, Pulmocort Respules®, in this patient population. Studies in this group utilized dry powder budesonide in attempts to establish an optimal treatment dosage. Nebulized budesonide was studied only in acute exacerbations, under supervised conditions in a hospital emergency department, clinical or inpatient hospital setting. There were no studies with a Medicare-aged population in the unsupervised home setting. Inhalation of dry power budesonide may not equate in a 1:1 dosage conversion to nebulized solution; however, no clinical studies were identified making this comparison. For dry powder inhaler, the studies reviewed indicate that maximum effect is achieved at 1000 μg/day (1.0 mg/day) or less and that greater dosage does not confer additional benefit.
CONCLUSION

Since the Medicare IOM Benefit Manual requires contractors to base off-label use coverage on standards of care or published medical literature, nebulized budesonide in the form of Pulmicort Respules® only meets the burden of evidence in the treatment of acute exacerbations of asthma or COPD in a supervised clinical setting. However, such a restriction, while consistent with CMS instructions, is not clinically reasonable for a class of medications with proven efficacy in treating patients with COPD and asthma. A more prudent and clinically acceptable approach would be, in the absence of studies providing a dry powder to nebulized solution dosage conversion, to accept the findings of the clinical literature based on the dry powder form of budesonide (Turbuhaler®) and conclude that there is no clinical benefit to administering over 1,000 μg (1.0 mg) per day.

Based on the clinical and scientific evidence, it is not reasonable and necessary to administer amounts of budesonide (J7626) via nebulized solution in excess of the published local coverage determination limit of 62 UOS per month (0.5 mg/UOS administered 2x/day x 31 days per month = 62 UOS per month).

BIBLIOGRAPHY

PULMICORT RESPULES Prescribing Information.

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