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PHARMACEUTICALS

Graceway Pharmaceuticals, LLC
222 Valley Creek Boulevard, Suite 300
Exton, Pennsylvania 19341
Phone: 267.948.0400
Fax: 267.948.0599

Corporate Headquarters
Bristol, Tennessee

March 11, 2008

Roger Citron
Montana Department of Public Health & Human Services
e-mail: rcitron@mt.gov and pdl@mt.gov

Dear Mr. Citron:

Your Graceway Pharmaceuticals Government Account Manager, Perry Johnson, has requested that Graceway Pharmaceuticals submit clinical information about Maxair® Autohaler® (pirbuterol acetate inhalation aerosol) for your review and recommendation. According to the information that Perry provided, you are reviewing the therapeutic class of "Short Acting Beta Agonist Inhalers" for future recommendation and will be discussing this class of drugs at an upcoming meeting of Montana Medicaid.

Graceway Pharmaceuticals is requesting that our product, Maxair Autohaler, be considered as a cost-effective addition to the Montana Medicaid PDL for patients who cannot use albuterol or are unable to use generic press-and-breathe inhalers.

Approved Indication

Maxair Autohaler is indicated for the prevention and reversal of bronchospasm in patients 12 years of age and older with reversible bronchospasm including asthma. It may be used with or without concurrent theophylline and/or corticosteroid therapy.

Product Description

Maxair Autohaler is a pressurized metered-dose aerosol unit for oral inhalation. It provides a fine-particle suspension of pirbuterol acetate, a beta-2 adrenergic agonist bronchodilator. The Maxair Autohaler unit is breath-actuated such that the medication is delivered automatically during inspiration without the need for the patient to coordinate actuation with inspiration. Each inhalation from Maxair Autohaler delivers 200 mcg of pirbuterol. There are 400 inhalations in each Maxair Autohaler compared to 200 inhalations of medication in generic albuterol press-and-breathe inhalers.

Pharmacology

Maxair Autohaler contains pirbuterol, a beta-agonist. *In vitro* studies and *in vivo* pharmacologic studies have demonstrated that pirbuterol has a preferential effect on beta-2 adrenergic receptors. *In vitro* animal experiments indicate that the relative selectivity of pirbuterol for pulmonary as opposed to cardiac tissue is 9 times greater than that for albuterol and 1500 times greater than that for isoproterenol.[1 *]

Clinical Efficacy

Maxair Autohaler (pirbuterol) inhalation aerosol is a highly effective, selective beta agonist[i] which has been shown as effective as press-and-breathe metered dose inhalers with spacers[ii] and as effective as nebulized albuterol for moderate asthma exacerbations (FEV_1 40-70% of predicted) in an emergency room setting.[iii] The Autohaler is a breath actuated drug delivery device that is easier to use correctly than conventional metered dose inhalers and is patient preferred[iv,v,vi,vii] For those who are not well coordinated in the use of an inhaler, the deposition of albuterol into the lungs with an Autohaler device is substantially and significantly better than that of albuterol with a conventional press-and-breathe metered dose inhaler.[viii,ix]

Comparisons

Maxair Autohaler is a unique alternative to albuterol. While inhaled albuterol has been adequate for many, there is an intensely loyal sector of patients who favor pirbuterol as their beta agonist and resist any efforts to return them to albuterol. For those for whom technique is a problem, the breath actuated Maxair Autohaler may provide better drug delivery. When one talks to patients, many report less palpitations, tachycardia, and muscular tremor as adverse events with pirbuterol compared to albuterol. While there are few data comparing pirbuterol to albuterol in this regard, there is one study showing pirbuterol has less stimulus to heart rate than salbutamol (albuterol),[x] and we would submit that patients should have the option of using pirbuterol, either as a first choice or as an alternative to albuterol. Certainly Maxair Autohaler is a mature product with an established and largely predictable adverse drug reaction profile and is unlikely to encounter the surprises that can occur with newer drugs.

Adverse Reactions

Pirbuterol has a relatively low incidence of cardiac side effects. The incidence of tachycardia and palpitations in patients during pirbuterol use is 1.2% and 1.7%, respectively. The most frequent non-cardiac adverse reactions reported in clinical studies are: nervousness (6.9%), tremor (6%), headache (2%), dizziness (1.2%), cough (1.2%), and nausea (1.7%).

Graceway Pharmaceuticals, the makers of Maxair Autohaler, would like to inform you that our product will remain available for the many patients that rely on pirbuterol delivered by the Maxair Autohaler device for their respiratory conditions. There has been some confusion regarding the new government rulings regarding CFC containing products, which include our product, and the way that the different products are packaged.

Following are some facts that may help clarify these issues:

- The Federal Register (April 4, 2005, Volume 70, Number 63; Rules and Regulations (Pages 17167-17192) indicates that the "essential use designation for CFC containing albuterol MDIs ends on December 31, 2008". This ruling **does not** affect pirbuterol MDIs. Maxair Autohaler is not affected by the removal of **albuterol MDI containing CFCs** and will continue to be available after December 31, 2008.

- It should be noted that the Maxair Autohaler is the **only** available pirbuterol containing inhaler. Product availability will NOT be affected by the removal of CFC containing albuterol MDIs on December 31, 2008.

- There is no CFC-free alternative to pirbuterol available at present.

- Graceway will continue to make Maxair Autohaler available to patients beyond December 31, 2008.

- Maxair Autohaler has 400 doses per canister and should provide rescue medication for an extended period (generally twice as long as 200 dose containers.)

- The breath-actuation function allows patients to use Maxair Autohaler without a spacer.

We would like to make sure you know that Maxair Autohaler will continue to be available in quantities to meet demand and at a reasonable net-effective cost to the state Medicaid program.

Summary

We believe there is a large subset of patients that are not able to use albuterol, generic or otherwise, because of the side effects experienced by these patients. Many of these patients find pirbuterol acetate (Maxair Autohaler) a better drug because it does not adversely affect them after normal therapy dosing. Most find the device easier to use, and the Maxair Autohaler is comparable in all measures of efficacy and safety to albuterol delivered with a conventional metered dose inhaler, plus a spacing device. Marginal hand-breath coordination with metered dose inhalers is a major cause of

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suboptimal metered dose inhaler therapy[xi] and is associated with overuse of inhaled beta agonists. This can be an important factor leading to hospitalization for asthma exacerbations.[11]

Maxair Autohaler is an excellent choice for a short-acting beta-agonist inhaler. Patients, who have difficulty coordinating inhaler actuation with inspiration due to physical disability, age, or any other reason, will particularly benefit from this product. Also when considering the economic value and the total cost of any medication, additional expenses such as those associated with inadequately controlled disease and visits to acute care facilities should all be considered in the total cost of patient therapy. The Maxair Autohaler has the potential to reduce these costs because it facilitates better management of pulmonary disorders, potentially keeping a subset of patients out of acute care facilities. In addition, Maxair Autohaler contains 400 doses of medication vs. the customary 200 with other inhaled beta-adrenergic agents.

In light of all these facts, Graceway Pharmaceuticals respectfully requests that Maxair Autohaler be added to the Montana Medicaid PDL without restrictions.

Thank you for your interest in Graceway Pharmaceuticals' products and for allowing rebuttal comments. If you have any further questions about Maxair Autohaler, please feel free to give me a call at (267) 948-0438.

Sincerely,

Arlene Santhouse, Pharm.D.
Director, Drug Surveillance and Information

References

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2 West Liberty Blvd. Suite 203 Malvern, PA 19355
Phone: 484-321-5600 Fax: 484-321-5656