

Essential Use Designation:

*Breath-actuated Pirbuterol
Acetate Inhalation Aerosol*

FDA Public Meeting
August 2, 2007



Graceway and Maxair[®] Autohaler[®]

- Graceway Pharmaceuticals, LLC
 - Founded in 2006 and headquartered in Bristol, TN
 - Specialty pharmaceutical company
 - Small Business – fewer than 400 employees
 - Acquired Maxair Autohaler in December 2006
 - Significantly impacted by the proposed rule
- Maxair Autohaler (pirbuterol acetate inhalation aerosol)
 - Only pirbuterol MDI
 - Only breath-actuated rescue inhaler
 - More than one-quarter million patients depend on the product
 - Graceway is financially prepared to fully support this product and its development

Why Are We Here?

- Maintain breath-actuated pirbuterol acetate (Maxair Autohaler) as an essential therapeutic option for patients
- Allow adequate time – beyond December 2009 – for the development and transition to a non-CFC version of Maxair Autohaler

Proposed Rule

- Proposed Rule
 - Graceway recognizes important environmental goals and competing policy issues
 - Committed to reformulation of Maxair Autohaler
 - Project cannot be completed by proposed effective date
 - Need time to ensure Maxair Autohaler remains available treatment option
- As the agency has emphasized throughout this process:

“The Agency’s primary focus is, and will remain, the health and safety of patients who currently use MDIs.”

J. Jenkins, Testimony Before the Senate Committee on Labor and Human Resources (April 2, 1998)

Timing and Public Response

- 60 day initial comment period
- Three weeks to notify patients and clinicians and register for public meeting
- Already, we have over 100 written comments detailing the experiences of:
 - Patients who failed on albuterol
 - Patients who depend on the unique delivery system
 - Patients with special conditions
- Thousands more mail-in comment cards from patients and physicians en route to FDA
- Detailed written comments from leading physicians
- Many who wanted to participate in the meeting could not

How Maxair Autohaler Meets the Medical Needs of Patients

- “Please keep Maxair on the market. I can not tolerate any inhaler with HFA due to sensitivity and allergic reaction. Maxair is the only product which I can use without any problem....” (S. Chan, 7/25/07)
- “There is no equivalent to Maxair and if this product was taken off the market my life would drastically change for the worse. Please, please, please let me know how I can help. My daughter also uses the product and she loves it.” (M. Florence, RN 7/27/07)
- “THIS IS THE ONLY INHALER THAT MY 9YEAR OLD CHILD CAN TAKE CORRECTLY BY HIMSELF WHEN HAVING AN ASTHMA ATTACK.” (E. Leonard, 7/22/07)
- “Three years ago, my doctor and I discovered that I am allergic to albuterol, which is a key component in all other rescue inhalers. After suffering a near-fatal allergic reaction to an albuterol inhaler, I switched to Maxair, which has successfully controlled my asthma ever since ... I am sincerely worried about what I will do if Maxair is removed from the market, as I will be left with no other options to treat my asthma in rescue situations!” (K. Ryzewski, 7/19/07)

Why Breath-Actuated Pirbuterol Acetate Is Essential

- Unique and important public health benefits
 - Rescue MDI for albuterol-intolerant patients
 - Only available breath-actuated rescue MDI
 - Over 15 years of safe and effective use
 - “Alternative” products will not be adequate for all Maxair Autohaler patients
- Substantial technical barriers to reformulation – including the economic barriers – require time to overcome
- Important health benefit outweighs minimal release of CFCs during transition to reformulated product

Unique and Important Public Health Benefits

- The Moiety – Pirbuterol Acetate
 - Chemically distinct from other beta 2 agonists, highly selective
 - Only albuterol/levalbuterol alternative for intolerant patients
- The Delivery System
 - Only breath-actuated rescue inhaler
 - Compact, portable, reliable, easy to use

The Proposed “Therapeutic Alternatives”

Proventil® HFA ProAir™ HFA Ventolin® HFA	(R/S)-albuterol sulfate	Press & Breathe
Xopenex HFA™	(R)-albuterol tartrate	Press & Breathe

Maxair Autohaler: Moiety

- Pirbuterol acetate is a different molecule than albuterol and its R-enantiomer
 - *In vitro* studies indicate that pirbuterol's selectivity for pulmonary (β 2) as opposed to cardiac (β 1) tissue is nine times greater than that of albuterol¹
 - *In vivo* dog study shows cardiovascular effects of pirbuterol “are clearly distinguished” from albuterol and that albuterol causes “more pronounced tachycardia”¹
- Labeling for proposed alternative products warns of “immediate hypersensitivity reactions,” including urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema²

¹ (Moore, *et al.*, J Pharm Exp Ther 1978)

² (Drug Labels: Proair HFA, Proventil HFA, Ventolin HFA, Xopenex HFA)

Short-Acting Bronchodilators: Labeling Comparison

	Tachycardia Adverse Events	Nervousness Adverse Events
Maxair Autohaler	1.2%	6.9%
Xopenex HFA	2.7%	9.6%
Proair HFA	3%	Proair label states that “In small cumulative dose studies, tremor, nervousness, and headache were the most frequently occurring adverse events.”
Proventil HFA	7%	7%
Ventolin HFA	10%	<10%

First-hand Patient Experience . . .

- “I am an asthma sufferer who also has Wolf Parkinson White's Syndrome, a birth defect that allows my heart to beat irregularly, sometimes over 200 beats per minute. Because of this condition I cannot use albuterol inhalers because they cause my heart to race, an understandably dangerous event. Maxair autohaler is the only inhaler I can use during asthma attacks or allergy season....” (A. Fussell, 7/23/07)
- “I use this product ... It is the only product that does not cause problems with my heart.” (N. Lloyd, 7/20/07)
- “Due to the reactions I get from all other rescue inhalers, Maxair is the only one that really works for me. The other brands cause me to start shaking enough to stop me from typing or driving.”
(D. Leister, 7/24/07)
- “I have been using Maxair for about two years now ... it was prescribed to me since it does not contain albuterol since I have some arrhythmia and the albuterol is harder on my heart according to the doctor.” (C. Cron, 7/19/07)

Clinician Experience . . .

“I am an allergist in Madison, Wi. I treat many asthma patients. I would estimate 30-40% of my asthma patients have Maxair as their rescue inhaler. The primary reason is most do not tolerate albuterol because of side effects such as tremors, palpitations, feeling jittery, etc. In my experience, I would estimate 75-80 % of patients who do not tolerate albuterol tolerate Maxair. This is critical for patients to have a rescue inhaler that they can tolerate for acute symptoms. Many of the patients experiencing side effects with albuterol would avoid using albuterol because of side effects, even though they were having problems breathing!”
(T. Puchner, M.D., July 27, 2006)

Rx Data Confirm Patient Reports

- Verispan Data, June 1, 2006 through May 31, 2007
 - More than 14,000 patients who were started on an albuterol product were switched to pirbuterol during this period
 - Of these, more than 4,000 moved from an albuterol HFA product to pirbuterol
- Moreover, during a brief supply shortage in 2005-06, 3M received hundreds of calls from Maxair Autohaler patients, including more than 20 spontaneous calls from patients with therapeutic failures on albuterol. Within this group, three reported an allergy to albuterol

The Maxair Autohaler Device

- The Maxair Autohaler is a proven and well established breath-actuated inhaler technology with 15 years of post market experience
- Ensures reliable dosing
- The device is easy to teach and easy to use
 - Pediatric
 - Geriatric
 - Movement-impaired, stroke victims, arthritics, etc.
- Importance of convenience/compliance factors in rescue product

Proven Breath-Actuated Technology Critical for Special Populations

For many patients, press-and-breathe MDIs are simply not an option:

“I have particular experience with elderly patients with severe arthritis or physical limitations from neurologic disease (e.g., Parkinson’s disease or stroke victims) that cannot use a conventional metered dose inhaler, regardless of the addition of a spacer device, and no matter how much teaching or training is provided.”

L. Rogers, M.D., FCCP, NYU School of Medicine August 1, 2007

“[T]he breath-actuated Maxair product is an essential treatment option, in particular for patients who are older or otherwise have trouble coordinating press-and-breathe inhalers.”

R. Panettieri, Jr., M.D., Univ. of Pennsylvania Medical Center (July 26, 2007)

Press-and-Breathe MDIs

- Press-and-breathe devices require the patient to coordinate actuation with the beginning of inspiration
- Even well trained patients may not be able to coordinate during severe bronchospasm
- For a rescue product, ease of use is not just a matter of convenience, it is critical:

Some of our patients are not able to use a regular metered-dose inhaler as they can't coordinate actuating and breathing. This device allows them to receive optimal dosage of their rescue medications without worrying about using the device correctly. In a life-threatening asthma attack, this could make a great difference.

ACAAI Comment (July 11, 2007) (emphasis added).

Spacers for Press-and-Breathe MDIs

- Introduce variability for HFA products; may not have been evaluated clinically
- Still requires coordination, dexterity; particular issue in special populations
- Lack of portability, inconvenience, particular problem for pediatric patients
- Barrier to use

Robert Anolik, M.D.



- Pediatric Allergist and Immunologist
- Asthma Specialist
 - Private practice with multiple locations in Philadelphia area
 - Board-certified in pediatrics and allergy/immunology
 - Fellow, AAAAI
 - Fellow, ACAAI
 - Served as Clinical Assistant Professor, Department of Allergy, Division of Pediatrics, University of Pennsylvania School of Medicine

Robert Anolik, M.D.



...In addition, there are some patients who clearly are intolerant of Albuterol. They have behavior side effects. They have difficulty sleeping. They get tachycardia. Parents will occasionally describe children as getting cranky and irritable, and it appears to occur much less commonly with Pirbuterol, with Maxair, and we often switch patients from Albuterol to Maxair to avoid those side effects...

I would suggest that the committee come spend some time in my office so that they can see the patients and talk to the patients or their families who have difficulty with Albuterol, either because of the device or because of the molecule, and then they can find out, in person, that there clearly is a need for this medication to stay on the market. It is very, very common for us to see patients who are unhappy if Maxair is unavailable. And we did have at least one instance in the past year or so, where there were shortages, and we received – or I should say my nurses at triage – literally, received hundreds of phone calls, families who were upset. What happened to Maxair? What am I going to use? I don't want to have to go back to Albuterol. What am I going to do for my child?

Hassan M. Makhzoumi, M.D.



- Pulmonologist
 - Chief of Pulmonary Medicine
 - St. Joseph Medical Center, Towson, Maryland
 - Also runs a private practice
 - Board-Certified
 - Pulmonary medicine
 - Critical care medicine
 - Internal medicine
 - Served as Instructor, Division of Respiratory Medicine, Johns Hopkins University School of Medicine

Hassan M. Makhzoumi, M.D.



First of all, as you know, the chemical agent in Maxair is pirbuterol. It's a rapid acting beta-agonist. It is rather specific for beta 2 as versus beta 1, which I like, doesn't affect the cardiovascular system a whole lot. But more importantly, it seems that that particular subtype of beta-agonist seems to work very well with a subset of my asthmatics in which albuterol does not seem to produce the same effects. To be very honest with you Maxair or pirbuterol is not my first choice. My first choice is albuterol. And I'd have to say six maybe seven out of ten asthmatics do well with that. Pirbuterol is what I turn to when asthmatics do not do well with albuterol, when asthmatics on albuterol seem to end up frequently in the emergency room and be admitted. Do not ask me why, I am not a scientist, I'm the clinician, I'm the practitioner, I'm the front lines here. What I can tell you is that about 30% of my asthmatics, particularly the young and the professional, seem to do far better with pirbuterol rescue therapy and lead much more of a controlled asthma life than those who use albuterol.

Asthma is on the rise. It is exponentially increasing. And we should be increasing our options to our physicians rather than taking away from them substances that seem to work. And work well.

I cannot over-emphasize the importance in this subset, of having their rescue therapy. Remember it's called rescue therapy. It means they can't breathe. We're not talking about long-term maintenance. We're talking about rescue therapy, and I would hate to look into the face of those people and tell them you're gonna be losing your rescue therapy.

Santiago R. Reyes, M.D.

- Pediatric pulmonologist
 - Private practice in Oklahoma City, Oklahoma
 - Board-certified
 - Pediatrics
 - Pediatric pulmonology
 - Fellow, American College of Chest Physicians
 - Investigator in numerous pediatric clinical trials



Santiago R. Reyes, M.D.



...some of my patients have difficulties in activating the MDI, the metered dose inhaler.

It happens that when you go to the pre-teenagers and the teenagers they of course do not like to take medications and a chamber is impractical for them, right, is big, is bulky, they don't like to keep them in the pockets, so they are not going to use it. The result of that is that perhaps they don't get enough medication down to the airways to accomplish the therapeutic purpose of the medications. So for me, when I started using the Maxair Autohaler it was like a prayer to be answered because these patients were now able to use the inhaler, the proper amount of medications, without having to carry around a chamber, so compliance improved tremendously.

I have also found that people using pirbuterol which is the Maxair, they don't experience some of the side effects like nervousness or shakiness that they do experience using the albuterol.

Mark Boguniewicz, M.D.

- Professor, Department of Pediatrics
- National Jewish Medical and Research Center
- University of Colorado School of Medicine
- Author of numerous journal articles and book chapters
- Editor/referee for numerous journals
- Member of numerous national allergy and immunology steering and review committees

Michael E. Wechsler, M.D., MMSc.

- Associate Physician, Pulmonary and Critical Care Division, Brigham and Women's Hospital
- Associate Director, The Asthma Research Center, Brigham and Women's Hospital
- Assistant Professor of Medicine, Harvard Medical School and Brigham and Women's Hospital
- Member, Steering Committee, National Institutes of Health Asthma Clinical Research Network
- Board-certified
 - Pulmonary medicine
 - Internal medicine
- Author of numerous journal articles and book chapters

Clifford W. Bassett, M.D.

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- Vice Chair, Public Education Committee, AAAAI
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- Faculty, New York University School of Medicine
- Assistant Clinical Professor of Medicine and Otolaryngology, The Long Island College Hospital, SUNY-HSCB, Brooklyn, NY
- Expert on asthma and exercise-induced asthma
- Published papers in
 - The Journal of Allergy and Clinical Immunology
 - Annals of Allergy, Asthma & Immunology
 - Pediatrics
 - Chest

Breath-Actuated Pirbuterol Acetate Remains Essential

- Only alternative moiety for patients who fail on albuterol/levalbuterol rescue MDIs
- Only available breath-actuated rescue inhaler
- Graceway is financially prepared and committed to developing Maxair Autohaler Non-ODS, however no one can complete this project by the proposed effective date
- Graceway is a Small Business, and the proposed rule will have a dramatically negative impact on both the product and the company
- Graceway looks forward to working with the agency to keep Maxair Autohaler available to patients