



## **Executive Summary**

### **Insurance Coverage for H1-Antihistamines: Implications for Quality Healthcare and Public Safety**

This position statement addresses patient access to other second generation antihistamines when loratadine becomes available over the counter (OTC). Allergic diseases that may require antihistamine therapy affect 10-25 % of the population and produce substantial morbidity. First generation antihistamines are effective for allergic rhinitis, conjunctivitis, urticaria and angioedema, but may cause sedation and performance impairment. Second generation antihistamines are associated with no (desloratadine, fexofenadine, loratadine) or less (azelastine, cetirizine, levocabastine) side effects and are currently usually recommended in preference to first generation antihistamines. Newer second generation antihistamines generally demonstrate greater clinical benefits than the older second generation antihistamine, loratadine. Clinical studies and experience also show that individuals do not necessarily respond similarly to specific agents within the second generation antihistamine class.

It is the position of our organizations that restricting access to other second generation antihistamines when loratadine becomes available OTC will adversely effect quality healthcare and public safety in the following ways:

1. Currently accepted standards of care will not be met if physicians and patients can only choose from a limited number of therapeutic options that may be less effective or less safe for an individual patient.
2. These policies may create economic barriers for patients and/or administrative hurdles for providers that hinder clinical decision-making and impede the physician-patient relationship
3. These policies may encourage many patients to self-medicate using OTC preparations and to increase their use of first generation antihistamines. In addition to individual sedation and performance impairment, this phenomenon could also impact public safety as the impaired individuals have contact with others at home, at work, at school, and on our highways.

4. Valuable professional advice from physician experts will more likely be omitted in patients who self-medicate, thereby limiting their access to many other potentially important aspects of optimal allergic diseases therapy.
5. Barriers to access to newer medications in order to reduce pharmaceutical costs in the short term may actually increase overall management costs for chronic diseases in the long run.

In conclusion, we believe that prescription policies limiting coverage/use of second generation antihistamines are medically inappropriate, in the long term more expensive, and are below current national standards of practice in the field of allergic and immunologic diseases. On behalf of our patients, their families, and their employers, we look forward to working with those interested in serving the needs of patients with allergic diseases and the general public to resolve these issues.



*November 18, 2002*

**Position Statement**

American Academy of Allergy, Asthma and Immunology (AAAAI)  
and  
American College of Allergy, Asthma and Immunology (ACAAI)  
and  
Joint Council of Allergy Asthma and Immunology (JCAAI)

**Insurance Coverage for H<sub>1</sub>-Antihistamines:**

**Implications for Quality Healthcare and Public Safety**

**1. Introduction**

AAAAI, ACAAI, and JCAAI are professional organizations whose membership includes physicians, scientists and other experts in the fields of allergic and respiratory diseases whose mission is to advance the knowledge and practice of allergy, asthma, and immunology for the benefit of the patients they serve.

Based on training and experience, the members of these organizations, through their professional societies, are uniquely qualified to identify and comment on issues which may impact on the availability of quality medical care for those who suffer from allergic diseases.

It has come to our attention that some health insurance carriers are considering policies which, if implemented, will substantially reduce/eliminate coverage and patient access to several second generation antihistamines and possibly other important allergy/asthma medications in the future. Representations

have been made by proponents of these policies regarding the lack of any adverse impact on quality of care.

Our professional experience and the scientific and medical literature suggest that these policies by their design will diminish access to recognized standards of treatment for millions of patients with allergic diseases. Our professional experience and the literature also suggest that these actions will not only diminish the quality of medical care for affected patients but also have significant health and safety implications for the general public.

The AAAAI, ACAAI, and JCAAI, as experts in the field of allergy, asthma and immunologic disorders, wish to clarify the clinical and scientific bases of concerns for the public's health and safety if these policies become commonplace in our society.

## **2. Patient Characteristics**

Allergic diseases, including allergic rhinitis, allergic conjunctivitis, asthma, atopic dermatitis, urticaria/angioedema and anaphylaxis, are estimated to affect 10-25% of the population<sup>1</sup>, and in children, up to 40%<sup>2</sup>. The duration of the symptoms may be limited to a single episode but often can last a lifetime.

Allergic rhinitis is the most common of these disorders with symptoms of itching, sneezing, nasal discharge and congestion. This inflammatory disease may also compromise an individual's quality of life<sup>3</sup>. In the majority of patients, the ability to sleep normally<sup>4</sup>, to be as productive at work<sup>5</sup>, and, for both children and adults, to perform as well as asymptomatic patients in a broad range of cognitive functions, is negatively impacted<sup>5,6</sup>. Furthermore, allergic rhinitis is a local manifestation of the systemic allergic condition, and comorbidities are common. In patients with eye symptoms due to allergies (allergic conjunctivitis), >95% have allergic rhinitis<sup>1</sup>. In patients with acute sinusitis, >25% have allergic rhinitis, and with chronic rhinosinusitis, 40% have allergic rhinitis<sup>1</sup>. Children who have otitis media with effusion

have an approximately 50% prevalence rate of allergic rhinitis<sup>7</sup>, and children and adults with asthma have allergic rhinitis in over 80% of cases<sup>1</sup>.

Urticarias (hives) and angioedemas (swelling) form a group of disorders characterized by transient welts and swellings that are frequently itchy, especially in the evenings and at night. Angioedema usually affects the lips and eyelids and sometimes the hands, feet and tongue. Occasionally it involves the larynx and gastrointestinal tract. The hives are distressing, and the angioedema can be worrisome for patients who fear the possibility of choking and death<sup>8</sup>. The Nottingham Profile questionnaire of general health revealed that the disability of patients with chronic urticaria, as evidenced by lack of energy, social isolation, emotional reactions and sleep disruption, was as severe as that experienced by patients awaiting triple coronary bypass surgery<sup>9</sup>.

### **3. Scientific and Clinical Issues**

Underlying the allergic diseases is a complex pathophysiologic process that includes chemical mediators, cytokines, chemokines, inflammatory cells and toxic proteins. One of the most important of these disease-causing mediators is histamine, which is especially important in causing allergic rhinitis and urticaria/angioedema. Over the last 60 years, a series of pharmacologic agents have been developed which have been called antihistamines. These substances, to varying degrees, have the capacities to compete with histamine for histamine type 1 receptors and reduce receptor-mediated activation, thus blocking the adverse effects of histamine. The newer, second generation antihistamines, have also been shown<sup>10</sup> to decrease the release of histamine and other mediators, such as PGD<sub>2</sub> and leukotrienes, from mast cells. Additional anti-inflammatory effects for some of the agents are suppression of cytokines/chemokines, adhesion molecule expression and cellular migration<sup>10</sup>.

Though the members of this class of medications are all referred to as “*antihistamines*”, they vary substantially in their pharmacology. Therefore, the selection of any one of these agents should be made,

especially for the large majority of patients who have persistent disease, in consultation with an experienced health care practitioner. This patient-physician partnership allows for appropriate diagnostic evaluation, therapeutic targeting and outcomes monitoring. Considerations when selecting an antihistamine primarily relate to risk-benefit ratios:

Adverse effects. First generation antihistamines, which became available between 1942 and 1982, have been documented to be associated with increased sleepiness from single doses<sup>11</sup>, persistence of sleepiness after multiple doses<sup>12</sup> and morning sleepiness following evening dosing<sup>13</sup>. In addition to drowsiness which the patient may not perceive, an even greater percentage of individuals experience mood, cognition and psychomotor performance impairment from these agents. These aspects of sedation have been identified in both self reports and sophisticated tests of psychomotor function, including learning and driving<sup>14,15,16</sup>. In light of these findings, the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology has stated:

*“...many patients may not perceive performance impairment that is associated with first generation antihistamines. Consequently, second generation antihistamines that are associated with less risk or no risk for these side effects should usually be considered...”<sup>17</sup>.*

Older antihistamines have other significant adverse effects, most of which are due to their non H<sub>1</sub>-receptor specific activities. The anticholinergic activities can lead to dry mouth, blurred vision, glaucoma, urinary retention and constipation. Increased weight gain, irritability and arrhythmias have been reported from other non-H<sub>1</sub> receptor effects of the first generation antihistamines<sup>18</sup>.

The major advantages of the second-generation antihistamines are their selectivity to the H<sub>1</sub>-receptor and their reduced central nervous system sedative effects. Desloratadine, ebastine, fexofenadine, loratadine and mizolastine are reported to have an incidence of sedation no different from placebo for

both somnolence and performance impairment<sup>19</sup>. Intranasal azelastine, cetirizine<sup>20</sup> and intranasal levocabastine are not considered to be entirely devoid of sedative effects.

Benefits. As with other therapeutic agents, consideration in the selection of an antihistamine relates to the risk-benefit ratio for a particular patient. Treatment with H<sub>1</sub>-receptor antagonists modifies the responses to histamine and allergen challenges in the skin, the airway and the general system. Comparisons have been made between the first and second generation H<sub>1</sub>-antihistamines in these areas. While these agents often have similar clinical efficacy, the second-generation antihistamines are clearly superior in terms of their sedative adverse effect profile, giving the newer agents a far more favorable therapeutic index in allergic rhinitis and chronic idiopathic urticaria.<sup>21,22,23</sup>

The newer second-generation antihistamines generally demonstrate greater clinical benefits than the older second generation antihistamine, loratadine. In skin histamine-induced wheal and flare suppression studies, fexofenadine<sup>24,25</sup>, cetirizine<sup>26</sup>, levocetirizine<sup>25</sup>, ebastine<sup>25,26</sup>, and mizolastine<sup>25</sup> all produce greater antihistaminic effects than loratadine. In environmental exposure unit studies<sup>27,28</sup>, park environmental exposure studies<sup>29</sup> and seasonal<sup>30</sup> and perennial<sup>31</sup> allergic rhinitis clinical trials, loratadine has been reported to have a significantly slower onset of action, significantly less ability to reduce total rhinoconjunctivitis symptoms, significantly less benefit on the individually focused complaints of nasal congestion and eye symptoms, and it provided significantly less improvement in the Rhinoconjunctivitis Quality of Life Questionnaire index than other newer second generation antihistamines. Clinical studies<sup>32</sup> and experience also show that individuals do not necessarily respond similarly to specific agents within the second generation antihistamine class.

#### **4. Quality and Socioeconomic Issues**

The members of the AAAAI, ACAAI, and JCAAI are practicing specialists caring for patients with allergic diseases. It is clear from the scientific data and our experience that the second-generation

antihistamines available in the United States, including azelastine, cetirizine, desloratadine, fexofenadine and loratadine, have far superior benefit/risk ratios as compared to older, first generation agents. For these reasons, they have been a major therapeutic advance and have substantially improved the quality of life for allergic patients.

It is the position of our organizations that the policies under consideration which restrict access to second generation antihistamines will negatively impact patients ability to receive optimal treatment for their allergic conditions in a number of ways:

- ◆ Commitment to Quality

Our organizations strongly assert that the treatment options made available to all allergy patients should reflect generally accepted standards of care to provide patients with the ability to choose the best available form of treatment to suit their individual needs.

- ◆ Limitation of Coverage = Limited Patient Access and Choice

It is the position of our organizations that any policy which decreases coverage for the second-generation antihistamines will effectively limit/deny access to several important medications which are central in the treatment of allergic disorders. Since not everyone responds to the same medication, limiting choice to a small number of generic medications will direct patients to choose from a limited number of therapeutic options which may be less effective and/or less safe.

- ◆ Barrier to Appropriate Clinical Decisions

Policies that limit patients' access to any of the appropriate allergy medications impede physicians' abilities to prescribe the most appropriate individualized treatment regimens.

Physicians must be allowed to present patients with all the options available to make an informed decision which best serves their needs. Policies that limit medication access create economic barriers for patients and administrative hurdles for physicians which hinder clinical decision making and impede the patient-physician relationship.

- ◆ Misrepresentations of Accepted Standards of Care

Several of these policies are being presented as meeting nationally accepted clinical guidelines for the management of allergic diseases. As authors of these standards, we assert this representation is inaccurate. In our view, any policy which directs patients to choose options which may not be most appropriate, safe or effective in order to obtain medication coverage from their health plan does not meet accepted standards of care for the management of allergic diseases as defined by experts in our specialty.

- ◆ Informed Decisions

Employer/purchasers and consumers of health care insurance who are making purchasing selections for their employees may mistakenly infer that health care professionals endorse these policies as meeting accepted clinical standards in the treatment of allergic diseases. This presents a significant ethical and legal obstacle to informed decision making/due diligence for purchasers of insurance in choosing coverage for their employees.

- ◆ Self-medication

These policies may encourage many patients to self medicate using over the counter (OTC) preparations. Currently, only first generation antihistamines, which are associated with sedation,

cognitive impairment and anticholinergic side effects, can be purchased without prescription. The availability of a single OTC nonsedating antihistamine does not guarantee that patients will respond to this product. The result may be the increased use of less safe, lower cost agents over antihistamines with demonstrably better benefit/risk profiles, thus impacting patient access to optimal quality therapy. Increased self-medication with sedating first generation antihistamines could also impact public safety as these impaired individuals have contact with others at home, at work, at school, and on our highways.<sup>16</sup>

◆ Professional Care

Valuable professional advice from physician experts will more likely be omitted in patients who self medicate. Proper diagnosis and treatment of allergic diseases is often a complex matter. Evaluation of symptom triggers, education regarding the nature of the disease, instructions to reduce the allergen burden, additional management of the comorbidities, and appropriate monitoring of a patient's progress may not be obtained outside the care of an experienced clinician. A doctor and patient together make the best decisions about health care treatment.

◆ Worker Productivity/ Liability –

Limiting access to the accepted standards of allergy care<sup>17,35</sup> has been associated with diminished health for the worker and increased liability in the workplace. These policies may increase the risk of injury for patients by driving them to more self-diagnosis and treatment. In a comparative study of patients whose initial antihistamine prescription was diphenhydramine or loratadine, the rate of injury in the first 30 days following diphenhydramine was > 2 times the rate

for loratadine<sup>34</sup>. The implications of employers choosing insurance plans which mandate limited choices for management of allergic diseases needs to be more fully addressed in a public forum.

- ◆ Increased Disease Burden / Cost to Society

Insurers who create barriers to access to newer medications in order to reduce pharmaceutical costs in the short term should recognize that such strategies may actually increase overall management costs for chronic diseases to their organizations and to society. This was documented recently in a paper by Frank Lichtenberg of the National Bureau of Economic Research and Graduate School of Business, Columbia University<sup>35</sup>. The benefits of using newer drugs in this study included decreased hospital stays, fewer doctor visits and lower non-drug expenditures. In times of limited healthcare resources, these inefficiencies should be of concern to everyone.

## **5. Conclusions**

The AAAAI, ACAAI, and JCAAI strongly assert that the treatment options made available to all patients with allergic and immunologic diseases should reflect accepted standards of medical care. Policies that limit patients' access to appropriate medications impede a physician's ability to prescribe the most appropriate treatment regimens.

Health care insurance consumers and purchasers, be they individuals or employers, need to be informed of policies that may adversely affect patient access to proper care. Policies that in their design present obstacles to the standards of quality treatment should not mistakenly be viewed as being endorsed by trained health care professionals. We believe that prescription policies limiting coverage/use of second generation antihistamines are medically inappropriate, in the long term more expensive, and are below current national standards of practice in the field of allergic and immunologic diseases.

On behalf of our patients, their families, and their employers, we look forward to working with those interested in serving the needs of patients with allergic diseases and the general public to resolve these issues.

## 6. References

1. Bousquet J, van Cauwenberge P, Khaltaev N, et al. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108:S147-336.
2. Wright AL, Holberg CJ, Martinez FD, et al. Epidemiology of physician-diagnosed allergic rhinitis in childhood. *Pediatrics* 1994;94:895-901.
3. Bousquet J, Bullinger M, Fayol C, et al. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire. *J Allergy Clin Immunol* 1994;94:182-8.
4. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy* 1991;21:77-83.
5. Tanner LA, Reilly M, Meltzer EO, et al. Effect of fexofenadine HCL on quality of life and work, classroom and daily activity impairment in patients with seasonal allergic rhinitis. *Am J Managed Care* 1999;5 (suppl):S235-47.
6. Wilken JA, Berkowitz R, Kane R. Decrements in vigilance and cognitive functioning associated with ragweed-induced allergic rhinitis. *Ann Allergy Asthma Immunol* 2002;89:372-80.
7. Tomonaga K, Kurono Y, Mogi G. The role of nasal allergy in otitis media with effusion - a clinical study. *Acta Otolaryngol* 1988;458 (suppl):41-7.
8. Kobza Black A, Greaves MW. Antihistamines in urticaria and angioedema. In: Simons FER, ed. *Histamine and H<sub>1</sub>-Antihistamines in Allergic Disease*, 2<sup>nd</sup> Edition, New York, NY: Marcel Dekker, 2002:249-86.

9. O'Donnell BF, Lawlor F, Simpson J, et al. The impact of chronic urticaria on the quality of life. *Br J Dermatol* 1997;136:197-201.
10. Assanasen P, Naclerio RM. Antiallergic antiinflammatory effects of H<sub>1</sub>-antihistamines in humans. In Simons FER, ed. *Histamine and H<sub>1</sub>-Antihistamines in Allergic Disease*, 2<sup>nd</sup> Edition, New York, NY: Marcel Dekker, 2002:101-39.
11. Roth J, Roehrs T, Koshorek G, et al. Sedative effects of antihistamines. *J Allergy Clin Immunol* 1987;80:94-8.
- 12.. Kay GG, Plotkin KE, Quig MB, et al. Sedating effects of AM/PM antihistamine dosing with evening chlorpheniramine and morning terfenadine. *Am J Man Care* 1997;3:1843-8.
13. Starbuck VN, Kay GG, Platenberg RC. Functional magnetic resonance imaging shows evidence of daytime sleepiness following evening dosing with chlorpheniramine. *J Allergy Clin Immunol* 1998;101:S97.
14. Kay GG, Berman B, Mockoviak SH, et al. Initial and steady-state effects of diphenhydramine and loratadine on sedation, cognition, mood, and psychomotor performance. *Arch Intern Med* 1997;157:2350-6.
15. Vuurman EFPM, van Veggel LMA, Uiterwijk MMC, et al. Seasonal allergic rhinitis and antihistamine effects on children's learning. *Ann Allergy* 1993;71:121-6.
16. Weiler JM, Bloomfield JR, Woodworth GG, et al. Effects of fexofenadine, diphenhydramine, and alcohol on driving performance. *Ann Intern Med* 2000;132:354-63.
17. Dykewicz MS, Fineman S, Skoner DP, et al. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol* 1998;81:478-518.
18. Kaliner MA. H<sub>1</sub>-Antihistamines in the Elderly. In Simons FER, ed. *Histamine and*

- H<sub>1</sub>-Antihistamines in Allergic Disease, 2<sup>nd</sup> Edition, New York, NY: Marcel Dekker, 2002:465-81.
19. Hindmarch I, Shamsi Z. Antihistamines: models to assess sedative properties, assessment of sedation, safety and other side-effects. *Clin Exp Allergy* 1999;29 (suppl 3):133-42.
  20. Howarth PH, Stern MA, Roi L, et al. Double-blind, placebo-controlled study comparing the efficacy and safety of fexofenadine hydrochloride (120 and 180mg once daily) and cetirizine in seasonal allergic rhinitis. *J Allergy Clin Immunol* 1999;104:927-33.
  21. Druce HM, Thoden WR, Mure P, et al. Brompheniramine, loratadine and placebo in allergic rhinitis: a placebo-controlled comparative clinical trial. *J Clin Pharmacol* 1998;38:382-9.
  22. Harvey RP, Comer C, Sanders B, et al. Model for outcomes assessment of antihistamine use for seasonal allergic rhinitis. *J Allergy Clin Immunol* 1996;97:1233-41.
  23. Monroe EW, Bernstein DI, Fox RW, et al. Relative efficacy and safety of loratadine, hydroxyzine and placebo in chronic idiopathic urticaria. *Arzneim Forsch Drug Res* 1992;42:1119-21.
  24. Simons FER, Simons KJ. Peripheral H<sub>1</sub>-blockade effect of fexofenadine. *Ann Allergy Asthma Immunol* 1997;79:530-2.
  25. Grant JA, Riethuisen J-M, Moulart B, DeVos C. A double-blind, randomized, single-dose, crossover comparison of levocetirizine with ebastine, fexofenadine, loratadine, mizolastine, and placebo: suppression of histamine-induced wheal-and-flare response during 24 hours in healthy male subjects. *Ann Allergy Asthma Immunol* 2002;88:190-7.
  26. Gispert J, Antonijoan R, Barbanoj M, et al. Efficacy of ebastine, cetirizine, and loratadine in histamine cutaneous challenges. *Ann Allergy Asthma Immunol* 2002;89:259-64.

27. Day JH, Briscoe M, Widlitz MD. Cetirizine, loratadine, or placebo in subjects with seasonal allergic rhinitis: Effects after controlled ragweed pollen challenge in an environmental exposure unit. *J Allergy Clin Immunol* 1998;101:638-45.
28. Day JH, Briscoe M, Rafeiro E, et al. Comparative onset of action and symptom relief with cetirizine, loratadine, or placebo in an environmental exposure unit in subjects with seasonal allergic rhinitis: confirmation of a test system. *Ann Allergy Asthma Immunol* 2001;87:474-81.
29. Meltzer EO, Weiler JM, Widlitz MD. Comparative outdoor study of the efficacy, onset and duration of action, and safety of cetirizine, loratadine and placebo for seasonal allergic rhinitis. *J Allergy Clin Immunol* 1996;97:617-26.
30. Van Cauwenberge P, Juniper E. Comparison of the efficacy, safety and quality of life provided by fexofenadine hydrochloride 120mg, loratadine 10mg and placebo administered once daily for the treatment of seasonal allergic rhinitis. *Clin Exp Allergy* 2000;30:891-9.
31. Freche C, Leynadier F, Horak F, et al. Mizolastine provides effective symptom relief in patients suffering from perennial allergic rhinitis: a double-blind, placebo-controlled study versus loratadine. *Ann Allergy Asthma Immunol* 2002;89:304-10.
32. Carlsen KH, Kramer J, Fagertun HE, et al. Loratadine and terfenadine in perennial allergic rhinitis. Treatment of nonresponders to the one drug with the other drug. *Allergy* 1993;48: 431-6.
33. Nelson HS, Rachelefsky GS, Chairs for the Task Force in Allergic Disorders. The Allergy Report, Overview of Allergic Diseases: diagnosis, management and barriers to care. The American Academy of Allergy, Asthma and Immunology, 2000
34. Finkle WD, Adams JL, Greenland S, Melmon KL. Increased risk of serious injury following an initial prescription for diphenhydramine. *Ann Allergy Asthma Immunol* 2002;89:244-50.

35. Lichtenberg F. Benefits and costs of newer drugs: an update. National Bureau of Economic Research, working paper 8996, Cambridge MA, June 2002.