BlueCross BlueShield Association

An Association of
Independent Blue Cross
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Dr. Steven Galson
Acting Director
Center for Drug Evaluation and Research, Food and Drug Administration
C/o Dockets Management Branch (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 01N-0397

Dear Dr. Galson:

The Blue Cross and Blue Shield Association (BCBSA) appreciates this opportunity to provide the Food and Drug Administration (FDA) with comments on transportation safety and potentially sedating or impairing medications.

BCBSA is a federation of 44 independent, locally operated Blue Cross and Blue Shield Plans (including Blue Cross of California, a subsidiary of Wellpoint Health Networks) that collectively provide health care coverage to nearly 80 million – more than one in four – Americans. Blue Cross and Blue Shield Plans have extensive experience in providing prescription drug coverage through a variety of products and delivery mechanisms designed to meet the quality and value demands of their customers.

Our interest in this issue stems from our support of Citizen Petition 98P-0610/CP1. This petition, submitted by Robert Seidman, Vice President of Pharmacy at Blue Cross of California (a subsidiary of Wellpoint Health Networks), requests that the FDA switch three antihistamines (fexofenadine, loratadine and cetirizine) from prescription to over-the-counter (OTC) status. These antihistamines are commonly known by their brand names Allegra, Claritin and Zyrtec, respectively.

BCBSA urges the FDA to adopt the May 11, 2001 recommendation of the Nonprescription and Pulmonary-Allergy Drugs Advisory Committees to make Allegra, Claritin, and Zyrtec available to consumers without a prescription based on the committees' findings that the drugs are safe and effective for OTC use. With regard to transportation safety, the antihistamines at issue in the Wellpoint petition have safety profiles that make them superior therapeutic alternatives to the potentially sedating or impairing medications in this therapeutic class currently available over-the-counter.

In addition, BCBSA supports the Wellpoint petition based on the marketing history of these drugs and the fact that they are in a therapeutic class already accepted for OTC availability (and have been sold OTC in Australia, Canada, European Union countries and New Zealand for several years).

BCBSA Recommendations

We urge the FDA to adopt the recommendation of its advisory committees to make Allegra, Claritin, and Zyrtec available to consumers without a prescription based on the committees' findings that the drugs are safe and effective for OTC use. By designating these drugs as OTC, the FDA will provide consumers a safe, effective, affordable and accessible therapeutic alternative to the currently available OTC antihistamines with known sedating/impairing effects that the NTSB has linked to fatal transportation accidents.[1] As the NTSB noted in its January 13, 2000 safety recommendation to the U.S. Department of Transportation, currently available antihistamines "are perhaps the most well-known of the over-the-counter medications with potentially impairing effects."[2]

There is a clear statutory presumption that a drug should be designated as OTC unless consumers are unable to appropriately diagnose their condition or correctly choose and safely use the remedy. As we stated in our testimony before the FDA at the agency's June 29, 2000 Part 15 hearing on the process for designation of drugs as OTC, BCBSA recommends that the FDA adopt a fundamental policy that a drug should be designated as prescription only where it is **not** safe and effective for the drug to be designated as OTC. In order to achieve this objective, BCBSA recommends that the FDA engage in a deliberate process for switching drugs from prescription to OTC status where such designation is safe and effective for the consumer, beginning with the drugs that are the subject of Wellpoint's petition.

Background

In July 1998, Wellpoint submitted to the FDA a citizen petition seeking OTC designation for the following brands of prescription antihistamines: Allegra, Allegra-D, Claritin, Claritin-D, and Zyrtec (21 CFR §10.30). These products have been approved for marketing by prescription in the United States since 1996 (Allegra), 1993 (Claritin) and 1995 (Zyrtec) for relief from symptoms associated with allergic rhinitis or other respiratory allergies such as runny nose, sneezing, itching of the nose or throat and itchy, watery eyes.

There are many antihistamine and antihistamine/decongestant products currently available OTC that were formerly available only through a prescription (e.g., Actifed, Benadryl, Chlor-Trimeton, Dimetapp, Tavist, etc.). These "first generation" antihistamine products are effective in providing relief from symptoms associated with allergic rhinitis or other respiratory allergies.

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[1] National Transportation Safety Board. 2000. *Greyhound Run-off-the-Road Accident, Burnt Cabins, PA*, June 20, 1998. Highway Accident Report NTSB/HAR-00/01. Washington, D.C.

[2] National Transportation Safety Board. 2000. Safety Recommendation, January 13, 2000.

However, first generation antihistamines also have side effects, including sedation and anticholinergic effects (dizziness, blurred vision, dry mouth, etc.). The NTSB highlighted the potentially impairing effects of currently available OTC antihistamines in its January 13, 2000 safety recommendation to the U.S. Department of Transportation.[3] Indeed, the NTSB investigation of a 1998 bus accident that resulted in seven fatalities found that the accident was caused in part by driver use of the first-generation OTC antihistamine diphenhydramine (commonly known by the brand name Benadryl).[4] Nevertheless, the FDA has determined that these products are safe for use by the lay public without the supervision of a licensed medical practitioner.

Allegra, Allegra-D, Claritin, Claritin-D, and Zyrtec are newer products or "second generation" antihistamines. Scientific evidence indicates that these second generation products are less sedating and exhibit a lower level of anticholinergic side effects than the first generation antihistamine products that are currently available OTC.

Safety Profile of Second Generation Antihistamines

The safety profiles of fexofenadine, loratadine and cetirizine compare favorably to first generation antihistamines.

Older generation antihistamines (such as chlorphenaramine and diphenhydramine) have a long history of OTC use for the treatment of allergic rhinitis and other related conditions. According to the FDA, "the efficacy of these drug products and the appropriateness of antihistamines in general for OTC marketing are not in question."[5]

Likewise, "the overall safety experience of the drugs [at issue in the Wellpoint petition] post-marketing has been favorable and the FDA is not questioning the safety of these agents for marketing."[6] The FDA's Center for Drug Evaluation and Research's OTC Switch Review Team conducted extensive review of worldwide safety information related to fexofenadine, loratadine and cetirizine in response to the Wellpoint petition and found no conclusive evidence of a causal relationship between use of fexofenadine or loratadine and serious adverse events.[7]

The Switch Review Team noted that while the occurrence rates of adverse events for first generation OTC antihistamines cannot be directly compared to those of fexofenadine, loratadine and cetirizine, these three newer products may offer "certain safety advantages" over the currently available OTC antihistamines, many of which are labeled as OTC sleep aids.[8] In contrast, the Switch Review Team found that "although generally

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[3] Ibid.
[4] National Transportation Safety Board. 2000. *Greyhound Run-off-the-Road Accident, Burnt Cabins, PA,* June 20, 1998. Highway Accident Report NTSB/HAR-00/01. Washington, D.C.
[5] FDA Overview of Issues for the Joint Nonprescription Drugs Advisory Committee and the Pulmonary-Allergy Drugs Advisory Committee, May 11, 2001, accessed from http://www.fda.gov/ohrms/dockets/ac/01/briefing/3737b_02_overview.html.
[6] Ibid.
[7] FDA Executive Summary on Risk Issues, accessed from http://www.fda.gov/ohrms/dockets/ac/01/briefing/3737b_03_risk.html.
[8] Ibid.

accepted as appropriate OTC drugs, the first generation antihistamines agents possess a number of safety concerns, some of which are serious, in addition to their widely recognized sedative and cognition-impairing properties."[9] The Switch Review Team further acknowledged that "a choice of appropriately labeled drug products in the OTC marketplace can be expected to aid the consumer to tailor product selection to one most appropriate to the intended use."[10]

Based on this evidence, on May 11, 2001 the FDA's Nonprescription and Pulmonary-Allergy Drugs Advisory Committees voted overwhelmingly that Claritin, Allegra and Zyrtec are safe and effective for use without a prescription.

Conclusion

BCBSA applauds the joint effort of the FDA and the National Transportation Safety Board (NTSB) to address the public health and safety issue of the role of sedating or impairing medications in transportation accidents.

To help ensure public health and safety, we urge the FDA adopt the May 11, 2001 recommendation of the Nonprescription and Pulmonary-Allergy Drugs Advisory Committees to make Allegra, Claritin, and Zyrtec available to consumers without a prescription based on the committees' findings that the drugs are safe and effective for OTC use. By designating these drugs as OTC, the FDA will provide consumers with greater access to safe, effective, and affordable therapeutic alternative to the currently available OTC antihistamines with known sedating/impairing effects.

BCBSA further recommends that the FDA adopt a fundamental policy that a drug should be designated as prescription only where it is **not** safe and effective for the drug to be designated as OTC. In order to achieve this objective, BCBSA recommends that the FDA engage in a deliberate process for switching drugs from prescription to OTC status where such designation is safe and effective for the consumer, beginning with the drugs that are the subject of Wellpoint's petition.

BCBSA commends the FDA for addressing this critical health care issue and supports the agency in its endeavors.

Sincerely,

Mary Nell Lehnhard
Senior Vice President
Office of Policy and Representation Sincerely

[9] Ibid.
[10] FDA Executive Summary on Risk Issues, accessed from http://www.fda.gov/ohrms/dockets/ac/01/briefing/3737b_03_risk.html.