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## Citizen Petition

The undersigned submits this petition to request the Commissioner of Food and Drugs to add a warning to the labeling of all nonprescription drugs products containing an ingredient with anticholinergic or histamine H1 inverse agonist effects.

## Action Requested

The Commissioner of Food and Drugs should add a warning to the labeling of all nonprescription drug products containing an ingredient with anticholinergic or histamine H1 inverse agonist effects that this product can cause a confusional state including impaired attention, disorientation, and decreased power of concentration. Furthermore, this impairment of thinking, added to the similar effect of other prescription and nonprescription drug products containing drugs with the same effects can increase the degree of impaired cognition leading to an acute confusional state or delirium, especially in older people who are more at risk for this effect than younger people.

## Statement of Grounds

As early as 1971, case reports were published suggesting that the confusional state following certain medications was due to the anticholinergic effect of the medicines. In 1972, Janowsky, et al, published a placebo-controlled study showing that the

confusional state caused by some drugs with anticholinergic effects was not affected by placebo but was improved by physostigmine confirming the anticholinergic mechanism for the confusion.

Tune, et al, (1992) assessed the 25 drugs most commonly prescribed for the elderly for anticholinergic activity and found 10 had levels associated with impairment in normal elderly subjects. The American Geriatrics Society 2012 Beers criteria for potentially inappropriate medications for older adults include 12 first generation antihistamine H1 receptor antagonists/reverse agonists, many of which are nonprescription drugs. All have central nervous system activity (Brunton LL, et al., 2011).

Recently, the concept of anticholinergic risk or burden has been developed to help understand the hazard of cognitive impairment from multiple medications, each having anticholinergic activity. Duran, et al, (2013) reviewed multiple published risk scales and identified 100 drugs as having this activity and a way to sum the anticholinergic activity of each to determine the anticholinergic burden for a medication regimen of multiple drugs. Many of the high potency anticholinergic drugs on the list are nonprescription antihistamines including chlorphenamine, cyproheptadine, diphenhydramine, and hydroxyzine.

Many population-based observational studies have been published showing worse performance in elderly taking drugs with anticholinergic activity than controls who don't take these drugs. Two examples are Ancelin, et al (2006) and Landi, et al (2007). The idea that anticholinergic drugs and especially first generation antihistamines cause cognitive impairment has been so well documented that it is now standard textbook content in geriatrics (Halter JB, et al, 2009), neurology (Roper and Samuels, 2009), and internal medicine (Goldman and Schafer, 2012).

There are two prospective controlled trials showing the same thing. The first trial by Sunderland, et al (1987) showed that patients with dementia of the Alzheimer type had marked impairment to 0.25 mg doses of scopolamine compared to matched elderly control subjects. The other study by Pomara, et al (2008) showed normal healthy elderly with the APOE E4 gene ( carriers) had impaired recall and mental slowness compared to non-carriers when given 2 mg trihexyphenidyl orally in a randomized double-blind placebo controlled study. These studies show that some subjects are at more risk than others for the confusion-causing effects of anticholinergic drugs.

Additional risk of prolonged anticholinergic drug therapy is an increase in the severity of amyloid plaque and neurofibrillary tangles seen in autopsied Parkinson's disease patients who were receiving anticholinergic drugs compared to those who had not received these drugs (Perry, et al, 2003). Another study found that subjects receiving 3 or more months of anticholinergic medications had an increased chance of becoming mildly cognitively impaired than those not receiving anticholinergic medications (Cai, et al, 2012).

### **Conclusion:**

The above data show that cognitive impairment can occur in patients receiving drugs with anticholinergic activity. The degree of impairment relates to the sensitivity of the person, often the age, and the total amount of anticholinergic activity received by the person. Most of the drugs with this activity are prescribed by physicians who can control the total amount of prescribed anticholinergic medication received by the patient. But potent first generation antihistamines are nonprescription and can be added to the regimen by anybody, usually without knowing that they may lead to a confusional state. When this occurs in an elderly person, the cause may be attributed to something else and not to the added "safe" over-the-counter drug product. For this reason, we think that all nonprescription drug products with anticholinergic activity or inverse agonist histamine H1 activity should have an appropriately worded warning that they can cause confusion, impaired attention, disorientation, and decreased power of concentration.

### **Environmental Impact.**

A warning in the labeling has no effect on the environment.

### **Economic Impact**

We do not see any likelihood of change in the money flow in any of the 6 areas of concern due to adding this warning to the label of the drug products described.

### **References**

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#### Certification

The undersigned certifies, that, to the best of knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petitioner.

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