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August 29, 2006

VIA HAND DELIVERY

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

CITIZEN PETITION

Dear Sir or Madam:

On behalf of our client, Rakoczy Molino Mazzochi Siwik LLP hereby submits this Citizen Petition, in quadruplicate, pursuant to 21 U.S.C. § 355(j) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as well as 21 C.F.R. §§ 10.20, 10.30, 320.21, 320.23.

A. ACTION REQUESTED

Petitioner respectfully requests that the U.S. Food and Drug Administration ("FDA") deny any request to switch ketotifen fumarate ophthalmic solution, 0.025%, from prescription status to over-the-counter ("OTC") status because it is an inappropriate candidate for nonprescription use. Specifically, Petitioner requests that FDA:

1. find that ketotifen fumarate ophthalmic solution, 0.025%, is for a medical condition that cannot be properly self-diagnosed by consumers;

2. find that ketotifen fumarate ophthalmic solution, 0.025%, only should be administered under a physician's supervision; and

3. not approve any applications for a nonprescription ketotifen fumarate ophthalmic solution, 0.025%.

Any other action by FDA would unnecessarily place the safety and health of millions of consumers at risk.

B. STATEMENT OF GROUNDS

I. Introduction.

Eyes, given their location in the human body, are highly exposed, vulnerable organs that serve a vital function. Therefore, FDA must take great care when considering an ophthalmic drug for a prescription-only to OTC switch.

Ketotifen fumarate ophthalmic solution, 0.025%, temporarily prevents the symptoms of allergic conjunctivitis. Because allergic conjunctivitis easily can be confused with bacterial conjunctivitis or viral conjunctivitis, it is crucial that a patient experiencing symptoms of allergic conjunctivitis obtain a proper diagnosis before receiving any treatment. As detailed below, a mistaken diagnosis could result in a patient administering the wrong medication for the conjunctivitis. Such an outcome, could lead to, at best, ineffective treatment of an ocular condition and, at worst, significant or permanent damage to the eyes.

Further, the availability of an OTC version of ketotifen fumarate may give rise to its overuse during self-medication. This could lead to the worsening of symptoms associated with allergic conjunctivitis, rather than their effective treatment. Requiring ketotifen fumarate to

retain its prescription-only status works to ensure that patients will receive the much-needed physician supervision while using this drug.

For these reasons, and those discussed below, ketotifen fumarate is not an appropriate candidate for a prescription-to-OTC switch. Thus, FDA should deny approval for any application or request to market ketotifen fumarate as an OTC drug.

A. Background Information On Ketotifen Fumarate.

Ketotifen fumarate ophthalmic solution, 0.025%, is a combination antihistamine/mast cell stabilizer product that prevents itching due to allergic conjunctivitis (commonly referred to as "pink eye"). (*See* Package Insert for Zaditor™ (ketotifen fumarate ophthalmic solution, 0.025%) at 1). Ketotifen "is a relatively selective, non-competitive histamine antagonist (H1-receptor) . . . [that] inhibits the release of mediators from cells involved in hypersensitivity reactions." (*See id.*). The mast cell stabilizers work to eliminate the outbreak of an allergic reaction by "inhibiting the degranulation of mast cells, preventing them from releasing histamine and other allergy mediators." ("Ocular Allergy Treatment," available at http://www.eyeupdate.com/pages/occular_allergy).

B. Prescription vs. Nonprescription Drugs.

The FFDCA requires a drug to have prescription status if "because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, [it] is not safe for use except under the supervision of a practitioner licensed by law to administer such drug." 21 U.S.C. § 353(b)(1)(A). FDA has interpreted this statutory language to require a drug to carry prescription status "if intervention of a learned intermediary is required for its proper use (administration and monitoring)." (3/26/02 Mem. from Charles E.

Lee, MD (Med. Off., Div. of Pulmonary & Allergy Drug Products) on Proposed OTC Switch for Loratadine). Furthermore, FDA regulations provide that a drug must be subject to prescription-dispensing requirements unless FDA determines that:

> such requirements are not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and [it] finds that the drug is *safe and effective for use in self-medication* as directed in proposed labeling.

21 C.F.R. § 310.200(b) (emphasis added).

Based upon the statutory and regulatory requirements regarding the prescription status of drugs, a major consideration in determining whether to permit the switch of a prescription drug to nonprescription status is whether consumers, on their own, can obtain the desired medical result without putting their safety at risk. (*See* "Now Available Without a Prescription," *FDA Consumer Magazine*, available at www.fda.gov/fdac). FDA must consider whether "patients can diagnose the condition themselves—or at least recognize the symptoms they want to treat—and whether routine medical examinations or laboratory tests are required for continued safe use of a drug." (*Id.*).

For the reasons set forth below, consumers may confuse the symptoms of bacterial conjunctivitis or viral conjunctivitis with those of allergic conjunctivitis. Further, physician supervision of a patient using ketotifen fumarate is necessary because prolonged use of the drug may cause or exacerbate the very symptoms it is intended to treat. Accordingly, FDA should continue to require that ketotifen fumarate be dispensed by prescription to ensure that patients receive a proper diagnosis and adequate physician supervision.

II. Ketotifen Fumarate Is Not An Appropriate Drug Candidate For OTC Status.

Even though ketotifen fumarate is considered a "safe" drug when it comes to the issue of toxicity, it does not necessarily follow that the ketotifen fumarate is an appropriate drug candidate for OTC status. For instance, a consumer could mistakenly diagnose a harmful eye infection as allergic conjunctivitis or could improperly use ketotifen fumarate for a prolonged period of time. Such misuse could have serious health consequences for the patient. Consequently, FDA should deny any application seeking to market ketotifen fumarate OTC.

A. A Consumer's Incorrect Self-Diagnosis Of Allergic Conjunctivitis Could Lead To Permanent Damage To The Eyes.

Allergic conjunctivitis can be difficult to distinguish from other types of conjunctivitis caused by infection, such as bacterial conjunctivitis or viral conjunctivitis. (*See* "Eye Allergies and Allergic Conjunctivitis," *Medem Medical Library*, available at http://www.medem.com/MedLB). Allergic, bacterial, and viral conjunctivitis all share similar symptoms such as redness, itching and swelling in the eye area. (*See id.*). A correct diagnosis is, however, critical because allergic, bacterial, and viral conjunctivitis each require different treatment. (*See id.*; "Allergic Conjunctivitis from WebMD," available at http://www.webmd.com ("It is important to find out whether . . . pink eye is caused by allergies or infection because each condition has different treatments.")). But given that these three types of conjunctivitis have common symptoms, a consumer understandably might have difficulty self-diagnosing the correct type of conjunctivitis. Indeed, physicians, themselves, sometimes have difficulty correctly diagnosing the cause of conjunctivitis. (*See, e.g.*, "Bacterial Conjunctivitis," Handbook of Ocular Disease Management, available at http://www.revoptom.com/handbook

(noting that physicians may mistake the symptoms of bacterial conjunctivitis for the symptoms of viral and allergic conjunctivitis and misdiagnose the condition)).

If a consumer mistakenly self-diagnoses his or her condition as allergic conjunctivitis, rather than bacterial or viral conjunctivitis, the conjunctivitis will not be properly treated. This could possibly lead to significant damage to the eye. For instance, a microbial infection in the mucous membrane of the eye's surface causes bacterial conjunctivitis. (*See* Marlin, David S., "Conjunctivitis, Bacterial," *eMedicine*, available at www.emedicine.com/OPH/topic88.htm). A failure to accurately diagnose bacterial conjunctivitis may, in some instances, lead to severe complications or even death due to the failure to recognize and treat the underlying disease. (*See id.*). For example, sepsis and meningitis—both life-threatening diseases—can cause bacterial conjunctivitis. (*See id.*). Needless to say, it is critical that a doctor properly diagnose bacterial conjunctivitis and promptly identify its underlying causes.

In the case of viral conjunctivitis, failure to make a proper diagnosis may lead to a more severe condition such as keratitis, an infection affecting the eye's cornea. (*See* "Viral Conjunctivitis," Handbook of Ocular Disease Management, available at www.revoptom.com/handbook; www.netdoctor.co.uk/diseases/facts/conjunctivitis.htm). Keratitis is the most common cause of infection-related corneal blindness in the United States. (*See* www.visionweb.com). Accordingly, as with bacterial conjunctivitis, it is crucial that viral conjunctivitis is correctly diagnosed and promptly treated. (*See id.*).

Doctors often treat bacterial and viral conjunctivitis using antibiotic or antiviral eye drops, and not antihistamines or mast cell stabilizers such as ketotitfen fumarate. Thus, a

consumer who mistakes bacterial or viral conjunctivitis for allergic conjunctivitis and uses ketotifen fumarate will not effectively treat the infection. (*See* Information on Ketotifen Fumarate, available at http://myhealth.barnesjewish.org/library/healthguide/en-us/drugguide (stating that ketotifen fumarate should not be used to treat bacterial, viral, or fungal infections of the eye)). Furthermore, the ineffective treatment and misdiagnosis of bacterial or viral conjunctivitis puts others at risk, as both conditions are contagious. (*See* www.stlukeseye.com/Conditions/Conjunctivitis.asp).

Given the importance of accurately diagnosing the cause of conjunctivitis, and the ease with which it can be misdiagnosed, ketotifen fumarate simply is not an appropriate candidate for a switch from prescription to OTC.

B. A Patient's Use Of Ketotifen Fumarate Requires Physician Supervision.

A physician must monitor a patient's treatment with ketotifen. While ophthalmic antihistamines are intended to treat the symptoms of allergic reactions, they may actually cause allergic reactions and ocular irritation. (*See* "Ocular Allergy Treatment"). For instance, routine use of OTC allergy drops can be "irritating to the ocular surface, . . . and may actually precipitate massive inflammation by lysing mast cell membranes when over dosed – *which they frequently are*." (*See* Epstein, Arthur B., "Off the Cuff: OTC Revisited," *Optometric Physician*, Vol. 3 No. 12 (Mar. 24, 2003), available at www.revoptom.com/archive) (emphasis added)). In fact, "to use OTC anti-allergy preparations may not be in [patients'] best interest since they may continue to self-medicate for a long time." (*See* "Ocular Allergy Treatment"). Further, it is known that possible side effects of ketotifen fumarate include eye redness and swelling, eye discharge, increased itching of the eyes and eye pain. (*See* Medline Plus Drug Information: Ketotifen

(Ophthalmic), available at www.nlm.nih.gov/medlineplus/druginfo; Package Insert for Zaditor™ at 3 (noting that adverse reactions during clinical trials included, *inter alia*, allergic reactions, burning or stinging, conjunctivitis, itching, and keratitis)). Thus, given that ophthalmic antihistamines may themselves cause allergic reactions and irritation, it is important that a physician have control over the length of a patient's exposure to the medication. (*See* "Ocular Allergy Treatment").

When determining whether to permit a prescription-to-OTC switch for a medication, FDA considers whether patients are able to "achieve the desired result without endangering their safety." (*See* "Now Available Without a Prescription"). In the case of ketotifen fumarate, prolonged self-medication may exacerbate the very symptoms for which the patient seeks treatment. Thus, it is clear that physician supervision is necessary, not only to prescribe the medication, but also to monitor its use. As such, FDA should not grant approval for an OTC version of ketotifen fumarate.

III. A Prescription-to-OTC Switch For Ketotifen Fumarate Will Pose A Financial Burden On Consumers.

Not only will the availability of an OTC version of ketotifen fumarate put the safety of consumer's at risk, it will impose a heavy financial burden on them.

First, a consumer's misdiagnosis of allergic conjunctivitis could lead to increased health expenditures. For example, a consumer who mistakes viral conjunctivitis for allergic conjunctivitis will not receive prompt treatment for his or her condition. Consequently, the condition could worsen and multiple trips to the physician for treatment may be necessary. In other words, it is financially less burdensome for a consumer to initially see a physician to obtain

a proper diagnosis before receiving treatment, rather than make multiple visits to the doctor's office for a condition that the consumer's misdiagnosis has made worse.

Second, medical insurance usually covers the payment (or at least lowers the cost) of prescription drugs. If ketotifen fumarate becomes OTC, consumers will likely have to pay between $50-60 for a 5mL bottle. (*See* "Handbook of Ocular Disease Management – Allergic Conjunctivitis," available at www.revoptom.com/handbook). Needless to say, these high prices would pose a burden on most consumers. Thus, it is safer and more cost-effective for ketotifen fumarate to retain prescription-only status.

IV. Conclusion.

FDA should deem ketotifen fumarate is not an appropriate drug for nonprescription use and, therefore, not approve any applications or requests for a prescription-to-OTC switch for ketotifen fumarate ophthalmic solution, 0.025%.

C. ENVIRONMENTAL IMPACT

Under 21 C.F.R. § 25.31(a), this petition qualifies for a categorical exemption from the requirement to submit an environmental assessment.

D. ECONOMIC IMPACT

According to 21 C.F.R. § 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of the petition.

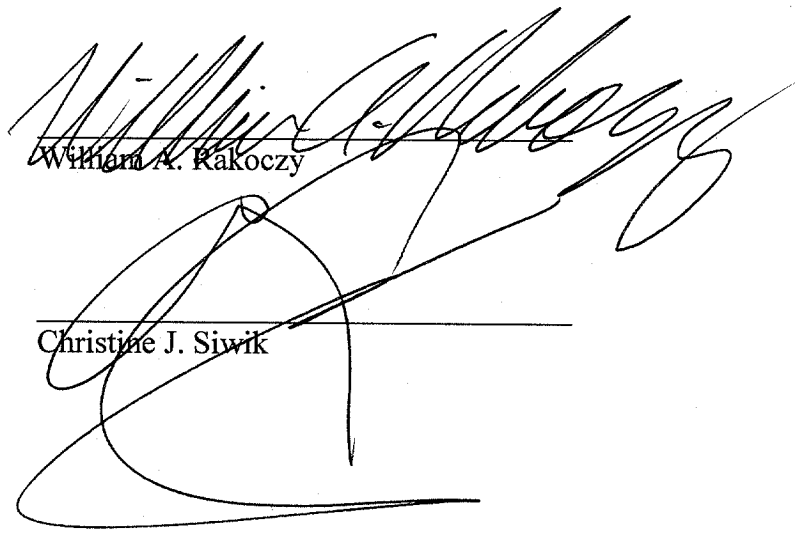
E. CERTIFICATION

The undersigned certifies, that, to the best 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 petition that are unfavorable to the petition.

Respectfully submitted,

RAKOCZY MOLINO MAZZOCHI SIWIK LLP



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