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December 15, 2006

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

CITIZEN PETITION

The undersigned submits this petition under 21CFR7.41, 21CFR10.20, 21CFR10.30, and 21CFR310.303 of the Code of Federal Regulations to request the Commissioner of Food and Drugs to require, at a minimum, long term safety studies or the recall of a topical combination product containing clindamycin phosphate 1.2% and tretinoin 0.025% (Ziana). In its current form, this combination presents the risk of violating 21CFR300.50 due to safety hazards secondary to the development of antibiotic resistance.

A. Action Requested

I respectfully urge that the Commissioner of the Food and Drug Administration (FDA) withdraw its approval of and recall all available stock of Ziana; or, at a minimum require the immediate initiation of long-term safety studies evaluating the incidence and prevalence of antibiotic resistance associated with Ziana usage.

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B. Statement of Grounds

Dermatologic research over the recent decade has proven that topical antibiotic use without benzoyl peroxide leads to the development of antibiotic resistant bacteria.[1] Antibiotic resistant bacteria possess the ability to confer resistance mechanisms to other bacterial species (e.g. *Staphylococcus).*[2,3] The reported incidence of resistant *Propionibacterium acnes* (*P acnes*) increased over 50% since the mid-1970s.[4] The growing incidence of antibiotic resistance is a worldwide health concern; all possible measures to reduce the incidence of resistance must be employed.[5]

Ziana delivers antibiotic therapy in the form of clindamycin 1.2% without the inclusion of benzoyl peroxide to inhibit the formation of antibiotic resistant *P acnes*. Topical clindamycin monotherapy (without benzoyl peroxide) has been shown to elicit resistant organisms as early as twelve (12) weeks into therapy with increases in resistant *P acnes* and coagulase-negative *staphylococci* of >1600% and >3500%, respectively.[6] Conversely, and in the same study, use of a combination product comprised of clindamycin and benzoyl peroxide reduced overall and resistant species of both *P acnes* and coagulase-negative *staphylococci.*[7]

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[1]Tan HH. Topical antibacterial treatments for acne vulgaris: comparative review and guide to selection. American Journal Clinical Dermatology, 2004; 5:79-84
[2] Ibid
[3] Levy, SB. Sci Amer. 1998; Mar: 46-53
[4]Eady, EA, et al. Dermatology 2003; 206:54–56
[5] www.cdc.gov
[6] Cunliffe WJ, Holland KT, Bojar R, Levy SF. (2002) "A randomized, double-blind comparison of clindamycin/benzoyl peroxide gel formulation and a matching clindamycin gel with respect to microbiologic activity and clinical efficacy in the topical treatment of acne vulgaris." *Clinical Therapeutics* 24(7), 1117-1133
[7] Ibid

In dermatology alone, the incidence of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) comprises as much as 50% of all *S aureus*–positive cultures in some regions.[8] While conclusive evidence identifying the causation of this increase is not yet available; it is known that any form of bacterial resistance has the ability to transfer to other species and effectively mutate to guard its survival.[9] Hence, all efforts to prevent the development of antibiotic resistance should be instituted. The only way to avoid the development of resistant when prescribing Ziana is to also prescribe a benzoyl peroxide product (refer to Tan reference on page 2). As there is no proven method to ensure that patients will comply with this dual therapy and medication compliance is inversely related to the complexity of the therapy[10] there is no assurance that this tactic will in any way reduce the risk of antibiotic resistance associated with Ziana.

(Full articles of the cited references in this section will be provided upon request.)

C. Environmental Impact

Pursuant to 21CFR25.31 this petition does not represent a hazardous impact to the environment as this petition is requesting a decreased, rather than increased, use of the active moiety and qualifies for a categorical exclusion.

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[8] Cohen P, Kurzrock R. Community-acquired methicillin-resistant *Staphylococcus aureus* skin infection: An emerging clinical problem. *J Am Acad Dermatol* 2004; 50:277-80
[9] Levy, SB. Sci Amer. 1998; Mar: 46-53
[10] Osterberg L, Terrence B. Adherence to Medication. NEJM. 2005; 353; 5:487-497

D. Economic Impact

Based upon scientific and clinical research data, this petition would have a favorable impact upon healthcare economics by supporting the global initiatives to reduce the incidence of antibiotic resistance, which often leads to more costly therapy as more potent antibiotics and additional therapies may be required. Additional information will be supplied as requested.

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 petitioner which are unfavorable to the petition.

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For the reasons listed herein, the FDA should immediately take action to halt the commercialization and sale of Ziana in the interest of both practitioners and patients alike. While the immediate effects of resistance are not as readily visible as serious drug reactions, the long-term impact will have lasting and deleterious effects upon the increased prevalence of antibiotic resistance. As there are multiple topical treatments for acne currently available on the market, such action will have no impact upon effective treatment for this patient population.

Respectfully submitted,

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