



**TRANSMITTED BY FACSIMILE**

David E.I. Pyott  
Chairman of the Board and Chief Executive Officer  
Allergan, Inc.  
2525 Dupont Drive  
Irvine, CA 92612

**RE: NDA# 21-794  
ACZONE® (dapsonsone) Gel, 5%  
MACMIS ID #17769**

**WARNING LETTER**

Dear Mr. Pyott:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a journal advertisement (APC021052008) for ACZONE® (dapsonsone) Gel, 5% (ACZONE) submitted under cover of Form FDA-2253 by Allergan, Inc. This journal advertisement is false or misleading because it overstates the efficacy of ACZONE, and omits material facts and important risk information associated with the use of the product. Therefore, this piece misbrands ACZONE in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(n) & 321(n), and FDA implementing regulations. 21 CFR 202.1(e)(5); (e)(6)(i); (e)(6)(vi) & (e)(7)(iii).

**Background**

According to the INDICATIONS AND USAGE section of its FDA-approved product labeling (PI), ACZONE Gel, 5%, is indicated “for the topical treatment of acne vulgaris.”

The DRUG INTERACTIONS section of the PI states (in relevant part):

Topical application of **ACZONE®** Gel followed by benzoyl peroxide in subjects with acne vulgaris resulted in a temporary local yellow or orange discoloration of the skin and facial hair (reported by 7 out of 95 subjects in a clinical study) with resolution in 4 to 57 days.

In addition, the CLINICAL STUDIES section of the PI presents efficacy results from the two randomized, double blind, vehicle controlled, clinical studies conducted to evaluate ACZONE (in pertinent part):

Efficacy was evaluated in terms of success on the Global Acne Assessment Score (no or minimal acne) and in the percent reduction in inflammatory, non-inflammatory, and total lesions.

The success rates on the Global Acne Assessment Score (no or minimal acne) at Week 12 are presented in Table 4.

**Table 4 - Success (No or Minimal Acne) on the Global Acne Assessment Score at Week 12**

|                                  | Study 1*        |                  | Study 2*        |                  |
|----------------------------------|-----------------|------------------|-----------------|------------------|
|                                  | ACZONE<br>N=699 | Vehicle<br>N=687 | ACZONE<br>N=729 | Vehicle<br>N=738 |
| Subjects with No or Minimal Acne | 291 (42%)       | 223 (32%)        | 253 (35%)       | 206 (28%)        |

\*Analysis excludes subjects classified with minimal acne at baseline

Table 5 presents the mean percent reduction in inflammatory, non-inflammatory, and total lesions from baseline to Week 12.

**Table 5 - Percent Reduction in Lesions from Baseline to Week 12**

|                  | Study 1         |                  | Study 2         |                  |
|------------------|-----------------|------------------|-----------------|------------------|
|                  | ACZONE<br>N=745 | Vehicle<br>N=740 | ACZONE<br>N=761 | Vehicle<br>N=764 |
| Inflammatory     | 46%             | 42%              | 48%             | 40%              |
| Non-Inflammatory | 31%             | 24%              | 30%             | 21%              |
| Total            | 38%             | 32%              | 37%             | 29%              |

### **Overstatement of Efficacy/Omission of Material Facts**

Promotional materials are misleading if they represent or suggest that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience. The journal ad claims that “[ACZONE] **Works fast** 24% reduction in inflammatory lesions at 2 weeks<sup>1</sup>” (emphasis in original). **This claim is a complete misrepresentation of the results of the Draelos study.** The wording clearly claims a substantial effect of ACZONE at 2 weeks. That article, which presents combined data for approximately 3,000 patients from two identically designed studies, did report very small differences between Dapsone gel and the vehicle gel of 7% for total lesions, 8% for non-inflammatory lesions, and 6% for inflammatory lesions at 12 weeks. However, at 2 weeks, the mean percent change in inflammatory lesion count in patients on dapsone gel was 24% and in patients on placebo was 22%, demonstrating an actual effect of 2%, which was not even nominally statistically significant (p=0.052). Furthermore, this finding was one of several possible analyses<sup>2</sup> that could be conducted with the 2 week data and was not pre-specified.

<sup>1</sup> Draelos ZD, Carter E, Maloney JM, et al; for the United States/Canada Dapsone Gel Study Group. Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris. *J Am Acad Dermatol.* 2007;56(3):439.e1-439.e10.

<sup>2</sup> For example, the difference for non-inflammatory lesions and for combined lesions at 2 weeks was just 1%, which is not close to significant.

Thus, this post-hoc analysis of inflammatory lesions cannot possibly be interpreted as showing a statistically significant result.

Additionally, the journal ad **grossly** overstates the efficacy of the drug by presenting only the most favorable result for ACZONE and ignoring the placebo response. Specifically, the journal ad describes the effect of ACZONE on inflammatory lesions as a “48% reduction in inflammatory lesions at 12 weeks.<sup>1</sup>” In fact, in the Draelos study, the placebo group had a 42% reduction in inflammatory lesions at week 12, for an actual effect of just 6%.

### **Omission of Risk Information**

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to the consequences that may result from the use of the drug as recommended or suggested by the materials. Although the journal ad includes information from the WARNING AND PRECAUTIONS and ADVERSE REACTIONS sections of the PI, it fails to include information from the DRUG INTERACTIONS section of the PI, which states “Topical application of **ACZONE**<sup>®</sup> Gel followed by benzoyl peroxide in subjects with acne vulgaris resulted in a temporary local yellow or orange discoloration of the skin and facial hair (reported by 7 out of 95 subjects in a clinical study) with resolution in 4 to 57 days.” By omitting this important risk information, the ad misleadingly suggests that ACZONE is safer than has been demonstrated by substantial evidence or substantial clinical experience.

### **Conclusion and Requested Action**

For the reasons discussed above, your professional journal advertisement misbrands ACZONE in violation of the Act, and FDA’s implementing regulations. 21 U.S.C. 352(n) and 321(n), and FDA implementing regulations. 21 CFR 202.1(e)(5); (e)(6)(i); (e)(6)(vi) & (e)(7)(iii).

DDMAC requests that Allergan, Inc. immediately cease the dissemination of violative promotional materials for ACZONE such as those described above. Please submit a written response to this letter on or before August 28, 2009, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) in use for ACZONE as of the date of this letter, identifying which of these materials contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS #17769 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for ACZONE comply with each

applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

*{See appended electronic signature page}*

Thomas W. Abrams, RPh, MBA  
Director  
Division of Drug Marketing,  
Advertising, and Communications

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THOMAS W ABRAMS  
08/17/2009