

**TRANSMITTED BY FACSIMILE**

Michelle Carpenter, JD, RAC
Executive Director, Regulatory Affairs
Dow Pharmaceutical Sciences, Inc.
1330 Redwood Way
Petaluma, CA 94954-1169

RE: NDA # 050819
ACANYA[®] (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/2.5%
MACMIS #20129

Dear Ms. Carpenter:

As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed Dow Pharmaceutical Sciences, Inc.'s (Dow) website for its drug product, ACANYA[®] (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/2.5% (Acanya).¹ This website overstates the efficacy of Acanya and omits and minimizes risks associated with the use of the drug. Therefore, this piece misbrands Acanya in violation of the Federal Food, Drug, and Cosmetic Act (Act), See 21 U.S.C. 352(a) & (n), 321(n); 21 CFR 202.1 (e)(5); (e)(6)(i) & (xviii).

Background

According to its FDA-approved product labeling (PI), Acanya is indicated for the topical treatment of acne vulgaris in patients 12 years or older.

The use of Acanya is contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis. Additionally, the WARNINGS and PRECAUTIONS section of the PI for Acanya states the following (in pertinent part):

Colitis

Systemic absorption of clindamycin has been demonstrated following topical use of clindamycin. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin. When significant diarrhea occurs, ACANYA Gel should be discontinued.

Severe colitis has occurred following oral and parenteral administration of clindamycin with an onset of up to several weeks following cessation of therapy.
. . . Severe colitis may result in death.

¹ Acanya website at <http://www.acanyagel.com/> (last accessed June 16, 2011).

Studies indicate toxin(s) produced by Clostridia is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. . . .

The WARNINGS AND PRECAUTIONS section of the PI also indicates that patients treated with Acanya should minimize sun exposure following drug application.

Common local adverse reactions associated with Acanya use are erythema, scaling, itching, burning, and stinging.

Additionally, the Postmarketing Experience section of the PI states the following (in pertinent part):

Anaphylaxis, as well as allergic reactions leading to hospitalizations, has been reported in postmarketing use of products containing clindamycin/benzoyl peroxide.

The PATIENT INFORMATION states the following (in pertinent part) (emphasis in original):

ACANYA Gel can cause serious side effects including:

Allergic reactions. Stop using ACANYA Gel, call your doctor and get help right away if you have any of the following symptoms:

- severe itching
- swelling of your face, eyes, lips, tongue or throat
- trouble breathing

The CLINICAL STUDIES section of the PI states the following (in pertinent part):

The safety and efficacy of once daily use of ACANYA Gel were assessed in two 12-week multi-center, randomized, blinded studies in patients 12 years and older with moderate to severe acne vulgaris. . . .The co-primary efficacy variables were:

- (1) Mean absolute change from baseline at week 12 in
 - Inflammatory lesion counts
 - Non-inflammatory lesion counts
- (2) Percent of subjects who had a two grade improvement from baseline on an Evaluator's Global Severity (EGS) score.

The results of Study 1 at week 12 are presented in the table below:

Study 1	ACANYA Gel N = 399	Clindamycin Gel N = 408	Benzoyl Peroxide Gel N = 406	Vehicle Gel N = 201
EGSS Clear or Almost Clear -----	115 (29%)	84 (21%)	76 (19%)	29 (14%)
2 grade reduction from baseline	131 (33%)	100 (25%)	96 (24%)	38 (19%)
Inflammatory Lesions: Mean absolute change	14.8	12.2	13.0	9.0
Mean percent (%) reduction	55.0%	47.1%	49.3%	34.5%
Non- Inflammatory Lesions: Mean absolute change	22.1	17.9	20.6	13.2
Mean percent (%) reduction	45.3%	38.0%	40.2%	28.6%

The results of Study 2 at week 12 are presented in the table below:

Study 2	ACANYA Gel N = 398	Clindamycin Gel N = 404	Benzoyl Peroxide Gel N = 403	Vehicle Gel N = 194
EGSS Clear or Almost Clear -----	113 (28%)	94 (23%)	94 (23%)	21 (11%)
2 grade reduction from baseline	147 (37%)	114 (28%)	114 (28%)	27 (14%)

Inflammatory Lesions:				
Mean absolute change	13.7	11.3	11.2	5.7
Mean percent (%) reduction	54.2%	45.3%	45.7%	23.3%
Non-Inflammatory Lesions:				
Mean absolute change	19.0	14.9	15.2	8.3
Mean percent (%) reduction	41.2%	34.3%	34.5%	19.2%

Overstatement of Efficacy

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 website makes the following claims (bolded emphasis in original; underlined emphasis added):

- **“How long does it take before I see results?”**

In clinical studies, some patients using Acanya Gel daily saw improvement as soon as 2 weeks, which continued throughout a 12-week treatment period. [Acanya Gel: About Acanya Gel webpage]

In addition, the Acanya Gel: Patient Before and After Use webpage includes a graphic depicting a 19-year-old patient’s acne continuously improving from baseline through weeks 4, 8, and 12. Such claims and presentations misleadingly imply a substantial effect of Acanya at 2 weeks and continued improvement throughout a 12-week treatment period. DDMAC is not aware of substantial evidence or substantial clinical experience to support such claims. According to the CLINICAL STUDIES section of the PI, the co-primary efficacy variables were the mean absolute change from baseline in inflammatory and non-inflammatory lesion counts and the percent of subjects who had a two-grade improvement from baseline on an EGS score at week 12. While patients were also evaluated at weeks 4 and 8, these earlier time points were not pre-specified endpoints in the clinical studies. Therefore, the clinical studies for Acanya do not provide substantial evidence or substantial clinical experience to support claims and presentations implying that Acanya works as early as 2 weeks and throughout a 12-week treatment period. If you have any evidence to support such claims and presentations please submit it to FDA for review.

Additionally, the top portion of the Acanya Gel: Consumer Home Page and all subsequent webpages include large images of faces (nose to chin) depicting completely clear, acne-free skin. The overwhelming impression conveyed by these images is that treatment with Acanya will result in complete clearing of acne, when this has not been demonstrated by substantial evidence or substantial clinical experience. According to the CLINICAL STUDIES section of the PI, the percent of patients who had clear (i.e., normal, clear skin with no evidence of acne) or almost clear skin (i.e., rare non-inflammatory lesions present, with rare non-inflamed papules) on the EGS scoring scale after treatment for 12 weeks in the two clinical studies were 29% and 28% for patients receiving Acanya versus 14% and 11% for the vehicle group in Study 1 and Study 2, respectively. We note that the Acanya Gel: Patient Before and After Use webpage presents before and after images of patients from clinical trials below the presentation cited above. These images are followed by the statements, "These unretouched photos represent actual clinical trial experience. As with all treatments, results may vary from person to person." However, this does not mitigate the misleading impression.

Omission of Material Facts and Minimization of Risk Information

Promotional materials are misleading if they fail to reveal material facts in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials.

The website presents numerous effectiveness claims for Acanya, but omits important material information associated with the use of the drug. While the website does communicate that patients with a history of inflammation of the colon (colitis) should not use Acanya, it fails to communicate that use of the drug is contraindicated in patients with a history of regional enteritis (Crohn's disease). In addition, while the website indicates that the drug "may cause diarrhea" and that patients who experience diarrhea should stop using Acanya immediately and call their doctor, it fails to convey that severe abdominal cramps are another symptom of colitis. Moreover, the website fails to convey that Acanya may cause serious allergic reactions which can include symptoms such as severe itching, swelling of the face, eyes, lips, tongue or throat, or trouble breathing, and that patients who experience allergic reactions should stop using Acanya and call their doctor right away. Finally, the website does not present risks in order of severity (e.g., Contraindications followed by Warnings and Precautions, and Adverse Reactions). The omission and minimization of this important risk information for Acanya misleadingly suggests that the drug is safer than has been demonstrated. We note that the website includes a link to the Full Prescribing Information, including the Patient Information; however this does not mitigate the misleading impression.

The website makes the following claim (bolded emphasis in original; underlined emphasis added):

- "**Acanya Gel is gentle to skin, too.**
The water-based gel contains no alcohol or detergents that may contribute to stinging or burning. . . ." [Acanya Gel: Consumer Home Page]

This claim minimizes the risks associated with the use of Acanya by implying that Acanya is gentle to the skin, when this has not been demonstrated by substantial evidence or substantial clinical experience. While we acknowledge that Acanya is a water-based gel and does not contain alcohol or detergents, according to the ADVERSE REACTIONS section of the PI, during treatment in clinical trials up to 8% and 2% of patients experienced mild and moderate burning, respectively. Additionally, during treatment in clinical trials, up to 6% and 1% of patients experienced mild and moderate stinging, respectively. Furthermore, mild and moderate erythema, scaling, and itching were also common local adverse reactions experienced by patients during treatment in clinical trials. Therefore, claims implying that Acanya is “gentle to skin” are misleading. We note the statement, “Side effects may include redness, scaling, itching, burning, and stinging” is presented at the bottom of the webpage. However, this does not mitigate the misleading impression conveyed by this claim.

Conclusion and Requested Action

For the reasons discussed above, the website misbrands Acanya in violation of the Act, See 21 U.S.C. 352(a) & (n), 321(n); 21 CFR 202.1 (e)(5); (e)(6)(i) & (xviii).

DDMAC requests that Dow immediately cease the dissemination of violative promotional materials for Acanya such as those described above. Please submit a written response to this letter on or before June 30, 2011, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Acanya that contain violations such as those described above, and explaining your plan for discontinuing use of such violative 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 # 20129 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 Acanya comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Sheetal Patel, PharmD
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHEETAL PATEL
06/16/2011