DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

David E.I. Pyott
President and Chief Executive Officer
Allergan, Inc.
PO Box 19534
Irvine, CA 92623-9534

RE: NDA #21-528
ACULAR LS® (ketorolac tromethamine ophthalmic solution) 0.4%
MACMIS #15238

WARNING LETTER

Dear Mr. Pyott:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional journal advertisement (ad) (4961273) for ACULAR LS® (ketorolac tromethamine ophthalmic solution) (Acular LS) submitted by Allergan, Inc. (Allergan) under cover of Form FDA 2253. The journal ad is false or misleading because it broadens the indication, presents unsubstantiated superiority claims, and omits important risk information for Acular LS. Thus, the journal ad misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §§ 352(n) & 321(n), and FDA implementing regulations. *See* 21 C.F.R §§ 202.1(e)(5)(i) & (iii); (6)(i) & (ii). These violations are concerning from a public health perspective because they suggest that Acular LS is safer or more effective than has been demonstrated, and they encourage the use of Acular LS in circumstances other than those for which the drug has been shown to be safe and effective.

Background

According to the Indications and Usage section of the FDA approved product labeling (PI):

> ACULAR LS ophthalmic solution is indicated for the reduction of ocular pain and burning/stinging following corneal refractive surgery.

The PI also explains that Acular LS is associated with several risks. It states (in pertinent part):

> **WARNINGS**
>
> There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory agents. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

With some nonsteroidal anti-inflammatory drugs there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

PRECAUTIONS

General: All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including ketorolac tromethamine ophthalmic solution, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDS and topical steroids may increase the potential for healing problems.

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored for corneal health.

Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Postmarketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.

It is recommended that ACULAR LS ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications, which may prolong bleeding time.

ADVERSE REACTIONS

The most frequently reported adverse reactions for ACULAR LS ophthalmic solution occurring in approximately 1 to 5% of the overall study population were conjunctival hyperemia, corneal infiltrates, headache, ocular edema and ocular pain.

The most frequent adverse events reported with the use of ketorolac tromethamine ophthalmic solutions have been transient stinging and burning on instillation. These events were reported by 20% - 40% of patients participating in these other clinical trials.

DOSAGE AND ADMINISTRATION

The recommended dose of ACULAR LS ophthalmic solution is one drop four times a day in the operated eye as needed for pain and burning/stinging for up to 4 days following corneal refractive surgery.

Broadening of Indication

The journal ad is false or misleading because it suggests that Acular LS is effective in a broader range of patients and conditions than has been demonstrated by substantial evidence or substantial clinical experience; in fact, it suggests that Acular LS is effective for an entirely new use. Specifically, the journal ad presents data intended to show a favorable result in a study of patients undergoing phacoemulsification, who received either Acular LS or Nevanac (nepafenac ophthalmic suspension) 0.1% 4 times daily for 2 days preoperatively plus 4 drops in the 90 minutes prior to surgery. This data includes a bar graph comparing the mean aqueous concentrations of Acular LS with the prodrug and active molecules of Nevanac—amfenac (active molecule) and nepafenac (prodrug molecule). Acular LS is depicted as having a greater mean aqueous concentration (1079 ng/mL) than nepafenac (588 ng/mL) and amfenac (365 ng/mL). The headline for the journal ad states (emphasis original):

"*ACULAR LS®: Outstanding Ocular* **PENETRATION**"

The graph is accompanied by the following claims (emphasis original):

- "In this study, ACULAR LS® achieved nearly **3-times greater penetration in patients** than the active metabolite of *Nevanac*™[1] (clinical significance unknown)"
- "In the same study, ACULAR LS® reduced prostaglandins below detectability in 62% of treated eyes vs 18% with *Nevanac*™ (N = 82)[1]"

This presentation is false or misleading for several reasons. First, its emphasis on the "mean aqueous concentrations" and "penetration" "achieved" with Acular LS in the study described above suggests that Acular LS is effective for use in patients undergoing phacoemulsification, when this is not supported by substantial evidence or substantial clinical experience. Acular LS is not approved for any use in patients undergoing phacoemulsification. Acular LS is only approved for corneal refractive surgery, which does not involve phacoemulsification.[2] The inclusion below these statements of the approved indication for Acular LS does not mitigate this misleading presentation.

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[1] Amico LM, Bucci FA Jr, Waterbury D. Aqueous PGE_2 inhibition of ketorolac 0.4% vs. nepafenac 0.1% in patients undergoing phacoemulsification. Poster presented at: Annual Meeting of the Association for Research in Vision and Ophthalmology: April 30-May 4, 2006; Fort Lauderdale, Fla.

[2] Phacoemulsification and corneal refractive surgery are two distinct and separate ocular surgeries. Corneal refractive surgery is an elective procedure performed on a healthy eye. Either a laser or a surgical blade is used to reshape the cornea and, therefore, change the refractive error. The eyeball itself is not penetrated. Phacoemulsification is a surgical procedure in which a cataract causing decreased visual acuity is removed. An incision is made into the eye and a machine using high-frequency ultrasonic waves emulsifies and removes the lens. Usually, an artificial intraocular lens is placed into the eye to provide the refractive power which the natural lens previously provided.

We also note that the data cited in support of this presentation do not constitute substantial evidence or substantial clinical experience supporting use in patients undergoing phacoemulsification. The abstract[1] cited describes a study that measured prostaglandin levels but did not evaluate the reduction of ocular inflammation in patients. Reduced prostaglandin levels have not been shown to correlate with clinical efficacy for reducing ocular inflammation. Furthermore, the study measured mean aqueous drug concentrations and drug penetration but did not evaluate any clinical endpoints, such as ocular pain or burning/stinging. Despite the journal ad's emphasis on "mean aqueous concentrations" and "penetration" "achieved," mean aqueous drug concentrations and penetration have not been shown to correlate with clinical efficacy.

Second, the claim "In the same study, ACULAR LS® reduced prostaglandins below detectability…" implies that Acular LS is effective for treating inflammation, when this is not supported by substantial evidence or substantial clinical experience. Acular LS is not approved to treat inflammation associated with any ocular surgery. Furthermore, as noted above, reduced prostaglandin levels have not been shown to correlate with clinical efficacy for reducing ocular inflammation.

Third, this presentation implies that Acular LS is safe and effective when used 4 times daily for 2 days preoperatively along with 4 drops in the 90 minutes prior to surgery, when this is not supported by substantial evidence or substantial clinical experience. Acular LS is only approved for use following surgery. Specifically, Acular LS is approved for the reduction of ocular pain and burning/stinging following corneal refractive surgery. In addition, the PI for Acular LS includes a precaution concerning the use of Acular LS more than 24 hours prior to surgery because postmarketing experience with topical NSAIDs suggests that such use may increase patient risk for the occurrence and severity of corneal adverse events.

Fourth, the comparison to Nevanac further misleadingly implies that Acular LS is approved for use in cataract surgery as Nevanac is. Nevanac is indicated for the treatment of pain and inflammation associated with cataract surgery, but Acular LS is indicated only for use as needed postoperatively for the reduction of ocular pain and burning/stinging following corneal refractive surgery. Cataract surgery and corneal refractive surgery are two distinct and separate ocular surgeries.

Finally, the claim "#1 Choice Among Ophthalmologists" adds to the misleading impression that Acular LS is approved for phacoemulsification. This claim, in the context of the totality of the presentation describing the use of Acular LS versus Nevanac in phacoemulsification discussed above, misleadingly suggests that Acular LS is an effective "choice" for use in phacoemulsification, when this is not supported by substantial evidence or substantial clinical experience.

Unsubstantiated Superiority Claims

The journal ad misleadingly suggests that Acular LS is superior to Nevanac for use in phacoemulsification, a use consistent with Nevanac's indication for cataract surgery, when this has not been demonstrated by substantial evidence or substantial clinical experience. Indeed, as noted above, Acular LS is not indicated for use in phacoemulsification. Specifically, the journal ad presents data comparing the mean aqueous concentrations, penetration, and prostaglandin levels of patients treated with Acular LS to patients treated with Nevanac. The phrase "clinical significance unknown" next to the statement that Acular LS "achieved nearly **3-times greater penetration in patients** than the active

metabolite of *Nevanac*" (emphasis original) does not mitigate this misleading presentation. As noted above, these measurements have not been shown to correlate with clinical efficacy. Therefore, the data[1] cited in support of this presentation do not constitute substantial evidence or substantial clinical experience that Acular LS is superior to Nevanac for any purpose.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made or with respect to the consequences that may result from the use of the drug as recommended or suggested in the materials. The journal ad contains information from the Acular LS PI regarding the contraindication, one of the precautions, and the less common adverse events. However, the ad fails to communicate several important risks associated with the use of Acular LS. The ad omits important warnings associated with Acular LS therapy regarding the potential for cross sensitivity reactions, potential for increased bleeding times, and increased bleeding of ocular tissues. It also omits information from the Precautions section of the PI regarding the risk of keratitis and the increased risk for corneal adverse events associated with certain concomitant disease states or conditions and factors such as duration of treatment. Finally, the journal ad omits the more common adverse reactions, including transient burning/stinging upon instillation. By omitting the most serious risks and common risks associated with the drug, the journal ad misleadingly suggests that Acular LS is safer than has been demonstrated.

Conclusion and Requested Action

For the reasons discussed above, the journal ad misbrands Acular LS in violation of the Act, 21 U.S.C. §§352(n) & 321(n), and FDA implementing regulations. *See* 21 C.F.R §§202.1(e)(5)(i) & (iii); (6)(i) & (ii).

DDMAC requests that Allergan immediately cease the dissemination of violative promotional materials for Acular LS such as those described above. Please submit a written response to this letter on or before June 11, 2007, stating whether you intend to comply with this request, listing all violative promotional materials for Acular LS the same as or similar to those described above, and explaining your plan for discontinuing use of such 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, or facsimile at 301-796-9878. In all future correspondence regarding this matter, please refer to MACMIS #15238 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 Acular LS 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 Abrams, R.Ph. M.B.A.
Director
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/

Thomas Abrams

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