DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Cary Rayment
President and Chief Executive Officer
Alcon, Inc.
C/O Alcon Research, Ltd.
6201 South Freeway R7-18
Fort Worth, TX 76134-2099

RE: NDA #21-862
Nevanac™ (nepafenac ophthalmic suspension) 0.1%
MACMIS ID #14150

WARNING LETTER

Dear Mr. Rayment:

The Division of Drug Marketing, Advertising, and Communications (DDMAC), in consultation with the Division of Anti-Infective and Ophthalmology Products, has reviewed a professional sales aid (NPF06500VS) for Nevanac™ (nepafenac ophthalmic suspension) (Nevanac) submitted by Alcon Research, Ltd. on behalf of Alcon, Inc. (Alcon) under cover of Form FDA 2253. This sales aid is false or misleading because it broadens the indication, presents unsubstantiated superiority claims, overstates the efficacy of Nevanac, omits risk information, and presents misleading safety claims, including a dosing claim that is inconsistent with the FDA approved product labeling (PI) for Nevanac. Thus, the sales aid misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §§352(a) & 321(n), and FDA implementing regulations. Cf. 21 C.F.R. §§202.1(e)(5)(iii); (6)(i); (ii) & (vii). These violations are concerning from a public health perspective because they suggest that Nevanac is safer or more effective than has been demonstrated, and they encourage use in circumstances other than those for which the drug has been shown to be safe and effective.

Background

According to the PI, Nevanac "is indicated for the treatment of pain and inflammation associated with cataract surgery." The PI contains several warnings and precautions. 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 including NEVANAC™, 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: Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including NEVANAC™, 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 including NEVANAC™ 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 1 day prior to surgery or use beyond 14 days post surgery may increase patient risk for occurrence and severity of corneal adverse events.

It is recommended that NEVANAC™ ophthalmic suspension be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

The PI contains the following information regarding the clinical pharmacology of Nevanac (in pertinent part):

After topical ocular dosing, nepafenac penetrates the cornea and is converted by ocular tissue hydrolases to amfenac, a nonsteroidal anti-inflammatory drug. Amfenac is thought to inhibit the action of prostaglandin H synthase (cyclooxygenase), an enzyme required for prostaglandin production.

In addition, the Dosage and Administration section of the PI states (in pertinent part):

Shake well before use. One drop of NEVANAC™ ophthalmic suspension should be applied to the affected eye(s) three-times-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period.

Prior Communications with DDMAC

DDMAC has expressed concerns regarding Alcon's promotional materials in earlier letters. On April 27, 2005, DDMAC sent Alcon Laboratories, Inc., an Alcon subsidiary, a warning letter for presenting

false or misleading claims for CIPRO® HC OTIC (ciprofloxacin hydrochloride and hydrocortisone otic suspension) on an Alcon website. This letter concerned promotional materials for CIPRO® HC OTIC that made unsubstantiated superiority claims, failed to reveal important risk information, and overstated the efficacy of the drug. In addition, on September 22, 2005, DDMAC sent Alcon Research, Ltd., an Alcon affiliate, an untitled letter regarding the failure to reveal material facts, unsubstantiated comparative and superiority claims, broadening of indication, minimization of risk and misleading dosing claims for another product, TRAVATAN® (travoprost ophthalmic solution). As we are now writing for the third time in an 18-month period with respect to false or misleading promotion for another of your prescription drugs, we are concerned that you are continuing to promote your prescription products in the United States in a violative manner.

Broadening of Indication

The sales aid suggests that Nevanac is effective in a broader range of patients than has been demonstrated by substantial evidence or substantial clinical experience. Specifically, on page three, the sales aid states, "Administration of nepafenac 0.1% suspension leads to significant suppression of PGE_2 synthesis in the posterior portion of the eye."[1] This claim is misleading because it suggests that Nevanac is effective for treating ocular conditions involving the posterior portion of the eye (*e.g.*, macular edema). The graphic representation comparing the prostaglandin reduction in the vitreous humor of nepafenac, diclofenac, and ketorolac that is presented next to this claim adds to the misleading suggestion that Nevanac is effective for ocular conditions involving the posterior portion of the eye, because the vitreous humor is located in the posterior portion of the eye. The PI, however, states Nevanac is indicated for treatment of pain and inflammation associated with cataract surgery. This indication only involves the anterior portion of the eye.

We note also that the reference cited in support of this claim does not constitute substantial evidence or substantial clinical experience. The reference cited contains favorable data or conclusions from nonclinical studies, in this instance studies using laboratory animals, in a way that suggests that the studies have clinical significance when in fact no such clinical significance has been demonstrated. Cf. 21 C.F.R. §202.1(e)(6)(vii).

The aforementioned issue is compounded by the following statement on the last page of the sales aid, "Prescribe NEVANAC™ suspension for excellent postoperative pain and inflammation control." This claim, in conjunction with the claims described above, is misleading because it suggests that the drug is effective for post-operative pain and inflammation after any eye surgery. FDA is not aware of substantial evidence or substantial clinical experience to support the use of Nevanac for the treatment of pain and inflammation associated with any eye surgery as opposed to cataract surgery.

Unsubstantiated Superiority Claims

The sales aid misleadingly suggests that Nevanac is superior to other drug therapies when this has not been demonstrated by substantial evidence or substantial clinical experience. Specifically, on page

[1] Kapin MA, Yanni JM, Brady MT, et al. Inflammation-mediated retinal edema in the rabbit is inhibited by topical nepafenac. *Inflammation*. 2003;27:295-305.

three, the piece contains a graph comparing the prostaglandin reduction in the vitreous humor of Nevanac with two other drugs in its class, diclofenac, and ketorolac.[1] The FDA is not aware of substantial evidence or substantial clinical experience that demonstrates the superiority of Nevanac over these two ophthalmic NSAIDS in postoperative pain and inflammation or prostaglandin inhibition. In fact, FDA is not aware of any comparison trials between Nevanac and any other ophthalmic NSAID. Nevanac was approved based on comparison to its vehicle, without any comparison to other active agents.

On pages two and three of the piece the sales aid misleadingly states:

- "NEVANAC™ suspension…is designed to activate at the sites of post-cataract inflammation, optimizing intraocular efficacy."[2] (page 2)
- "Superior efficacy in both early and late postoperative periods" (page 3)
- "NEVANAC™ suspension delivers superior prostaglandin inhibition"[1] (page 3)

These claims and presentations also are false or misleading because they suggest that Nevanac is superior to other agents for postoperative pain and inflammation, when no evidence is available showing that this is the case. As noted above, the FDA is not aware of any comparison trials between Nevanac and any other ophthalmic NSAID. The references cited for the first and third claims above contain favorable data or conclusions based on nonclinical studies using laboratory animals. The claims that refer to these references misleadingly suggest that the studies have clinical significance when in fact no such clinical significance has been demonstrated. Animal data cannot be presumed to predict clinical efficacy findings in humans. The disclosure on page three that the studies were conducted in animals does not mitigate the misleading implication that Nevanac is superior to other agents for preventing post-surgical inflammation in humans.

Overstatement of Efficacy

Page three of the sales aid contains a graph entitled "Percent Clinical Cures By Visit" next to which there is a bullet stating ">80% experienced clinical cures without use of steroids."[3] This presentation is misleading because the clinical cure rates presented in the graph are greater than has been demonstrated by substantial evidence or substantial clinical experience. The primary endpoint of the study that is cited to support the graph was "clinical cure" defined as 0 cells + 0 flare (which is the standard measurement of clinical cure). However, in the presentation, the definition used was 0-5 cells plus 0 flare. This definition was not pre-specified in the study cited and is a post-hoc analysis.

Consequently, the clinical cure rates shown in the sales aid are greater than those found in the study where the pre-specified endpoint was used. This is why, for example, the reference cited to support this presentation states that the clinical cure rate at day 14 is only 62.6% based on a clinical cure definition of 0 cells + 0 flare rather than > 80%, as presented in the piece.

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[2] Ke T-L, Graff G, Spellman JM, Yanni JM. Nepafenac, a unique nonsteroidal prodrug with potential utility in the treatment of trauma-induced ocular inflammation, II: in vitro bioactivation and permeation of external ocular barriers. *Inflammation.* 2004;24:371-384.

[3] Lindstrom R, Kim T. Ocular permeation and inhibition of retinal inflammation: an examination of data and expert opinion on the clinical utility of nepafenac. *Curr Med Res Opin.* 2006;2:397-404.

Omission of Risk

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. Although the sales aid contains information regarding the contraindication and most common and less severe adverse events, it fails to communicate the most serious warnings and precautions associated with Nevanac therapy, such as the potential for cross sensitivity reactions, increased bleeding times, delay of healing, keratitis, and other corneal adverse events. By omitting the most serious risks associated with the drug, the sales aid misleadingly suggests that Nevanac is safer than has been demonstrated.

Misleading Safety Presentations

Page four of the sales aid also presents the claim, "The excellent safety of NEVANAC™ suspension has been demonstrated *in vivo*[*] at concentrations up to 1.5%, dosing regimens up to 8 drops daily, and at periods up to 6 months."[4-6] This claim is misleading because the references cited to support it are studies conducted in animals. While there may be reasons to point out that doses in excess of those recommended are tolerated in animals, this presentation misleadingly suggests that the use of such doses is appropriate or recommended in patients. Such a suggestion is inconsistent with the PI, which recommends use of the 0.1% suspension three times daily for one day prior to surgery, continued on the day of surgery and through the first two weeks of the postoperative period for the treatment of pain and inflammation. The PI also contains a precaution stating that use beyond 14 days post surgery may increase patient risk for occurrence and severity of corneal adverse events. While we note that the footnote states that the studies were conducted in animals, this disclosure does not mitigate the misleading presentation.

Finally, page four of the sales aid also contains the claim, "Proven safe and well tolerated throughout *in vivo*[*] ocular tissues with no delays in wound healing."[4-6] This claim is misleading because it directly contradicts the Precautions section of the PI, which contains the general precaution that NSAIDS, including Nevanac, may slow or delay healing. Given that the sales aid fails to disclose this risk, this misleading claim is even more concerning.

Conclusion and Requested Actions

For the reasons discussed above, the sales aid broadens the indication, presents unsubstantiated superiority claims, overstates the efficacy of Nevanac, omits risk information, and presents misleading

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[4]Walker LM, Rice RL, Heaton JD, Hackett RB, Munger RJ, Hiddemen JW. Ocular effects of nepafenac ophthalmic suspension following three months of topical ocular administration to cynomolgus monkeys. Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 3, 2005; Fort Lauderdale, Fla.

[5]Heaton J, Hiddemen JW, Hackett RB, Rice RL, Gruebbel MM. Ocular effects of nepafenac ophthalmic suspension following six months of topical ocular administration to pigmented rabbits. Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 3, 2005; Fort Lauderdale, Fla.

[6]McGee DH, Heaton JD, Gruebbel MM, Hacket RB, Rice RL, Hiddemen JW. Ocular effects of nepafenac ophthalmic suspension in New Zealand white rabbits undergoing partial corneal incisions. Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 3, 2005; Fort Lauderdale, Fla.

safety claims, including a dosing claim that is inconsistent with the PI. Accordingly, the sales aid misbrands Nevanac in violation of the Act (21 U.S.C. §§352(a) & 321(n)) and FDA implementing regulations. Cf. 21 C.F.R. §§202.1(e)(5)(iii); (6)(i); (ii) & (vii).

DDMAC requests that Alcon immediately cease the dissemination of violative promotional materials for Nevanac such as those described above. Please submit a written response to this letter on or before November 3, 2006, stating whether you intend to comply with this request, listing all violative promotional materials for Nevanac such as 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 Nevanac promotional materials. Finally, we encourage you to review your promotional materials for all of your prescription products that Alcon promotes in the United States and to discontinue or revise any materials with the same or similar violations, and request that your response address this issue as well.

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 by facsimile at (301) 796-9877. In all future correspondence regarding this matter, please refer to the MACMIS ID #14150, 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 Nevanac 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, 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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