DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED VIA FACSIMILE

Cary R. Rayment
President and Chief Executive Officer
Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, TX 76134-2099

Re: NDA 21-537
Ciprodex® (ciprofloxacin 0.3% and dexamethasone 0.1%) Sterile Otic Suspension
MACMIS # 13836

WARNING LETTER

Dear Mr. Rayment:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a Retail Sell Sheet (CDX05505VS) and Sales Aid (CDX05503VS) for Ciprodex (ciprofloxacin 0.3% and dexamethasone 0.1%) Sterile Otic Suspension (Ciprodex), submitted by Alcon Laboratories, Inc. (Alcon) under cover of Form-FDA 2253. Both the retail sell sheet and sales aid omit material facts about Ciprodex, including important risk information and limits to Ciprodex's indication; the sales aid also makes numerous unsubstantiated superiority claims. Therefore, the materials misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§352(a) and 321(n). These violations are concerning from a public health perspective because they suggest that Ciprodex 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

The Indications and Usage section of the FDA-approved product labeling (PI) states (emphasis original):

> CIPRODEX® Otic is indicated for the treatment of infections caused by susceptible isolates of the designated microorganisms in the specific conditions listed below:
>
> **Acute Otitis Media** in pediatric patients (age 6 months and older) with tympanostomy tubes due to *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and *Pseudomonas aeruginosa*.
>
> **Acute Otitis Externa** in pediatric (age 6 months and older), adult and elderly patients due to *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

The PI contains important contraindications, warnings, precautions, and adverse reactions. It states (in pertinent part):

> **CONTRAINDICATIONS**
>
> CIPRODEX® Otic is contraindicated in patients with a history of hypersensitivity to ciprofloxacin, to other quinolones, or to any of the components in this medication. Use of this product is contraindicated in viral infections of the external canal including herpes simplex infections.
>
> **WARNINGS**
>
> **FOR OTIC USE ONLY**
> (This product is not approved for ophthalmic use.)
>
> **NOT FOR INJECTION**
>
> CIPRODEX® Otic should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones. Serious acute hypersensitivity reactions may require immediate emergency treatment.
>
> **PRECAUTIONS**
>
> As with other antibacterial preparations, use of this product may result in overgrowth of nonsusceptible organisms, including yeast and fungi. If the infection is not improved after one week of treatment, cultures should be obtained to guide further treatment. If otorrhea persists after a full course of therapy, or if two or more episodes of otorrhea occur within six months, further evaluation is recommended to exclude an underlying condition such as cholesteatoma, foreign body, or a tumor.
>
> The systemic administration of quinolones, including ciprofloxacin at doses much higher than given or absorbed by the otic route, has led to lesions or erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species.

Furthermore, the PI indicates that the most common adverse events associated with Ciprodex include ear pain, ear precipitate (residue), and irritability (in acute otitis media pediatric patients with tympanostomy tubes), and ear pruritis, ear debris and superimposed ear infection (in acute otitis externa patients).

Omission of Material Facts – Retail Sell Sheet

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 consequences that may result from the use of the drug as recommended or suggested by the materials. The retail sell sheet presents effectiveness

claims for Ciprodex, including that it is "approved for the treatment of acute otitis media with tympanostomy tubes and acute otitis externa" and "indicated for patients 6 months and older."

However, the main page of the sell sheet entirely omits risk information, including the most serious and frequently occurring risks associated with the drug.

The retail sell sheet also fails to accurately set forth the complete indication for Ciprodex, including material limitations to the indication. Specifically, the retail sell sheet claims Ciprodex is "approved for the treatment of acute otitis media with tympanostomy tubes and acute otitis externa." This claim misleadingly broadens the drug's indication by failing to reveal, for example, that it is only approved for use in the treatment of certain susceptible isolates of the designated microorganisms causing acute otitis media and acute otitis externa infections. Specifically, Ciprodex is only approved for the treatment of acute otitis media due to *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and *Pseudomonas aeruginosa* and the treatment of acute otitis externa due to *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

Unsubstantiated Superiority Claims – Sales Aid

The sales aid presents numerous false or misleading claims and presentations regarding the superiority of Ciprodex over Cortisporin Otic (neomycin 0.35%, polymyxin B 10,000 IU/mL, hydrocortisone 1%) (Cortisporin).

First, the sales aid makes false or misleading claims and presentations regarding the superiority of Ciprodex over Cortisporin with respect to its efficacy. The first page of the sales aid, which is entitled "MISSING SOMETHING?" (emphasis original), states "Don't Miss the Boat: CIPRODEX® Otic Cures More Otitis Externa Patients than CORTISPORIN* Otic[1]". The second page is entitled "Soak This Up: For More Cures, Reduce Pain and Inflammation Fast" and contains a graph presenting a comparison between the two drugs with respect to pain relief, as discussed below. The last page of the sales aid contains a chart entitled "Proven Results in Otitis Externa" which favorably compares Ciprodex to Cortisporin, as discussed in more detail below. Finally, the tagline "All together better" is stated three times in the piece. These claims and presentations are false or misleading because they suggest that Ciprodex is more efficacious than Cortisporin when this has not been demonstrated by substantial evidence or substantial clinical experience. The reference cited is inadequate to support claims of superior efficacy because there is no significant difference in cure rates between the Ciprodex treatment groups and the Cortisporin treatment groups for the two clinical studies cited in the PI, 87% and 94% versus 84% and 89%, respectively.

Second, as indicated above, the sales aid makes false or misleading claims regarding the superiority of Ciprodex over Cortisporin with respect to pain relief. For example, the second page of the aid states "Don't rock the boat: less pain by day 2[2]" [reference 1 below] and goes on to state:

- "In a recent clinical study, a significantly higher number of otitis externa patients using CIPRODEX® Otic reported less pain by day two than patients using CORTISPORIN Otic[2]" [reference 1 below]
- "Patients using CIPRODEX® Otic reported significantly less severe pain in the first 12 hours compared to patients treated with CORTISPORIN Otic[3]" [reference 2 below]

The second page also contains a graph entitled "More Patients Report Less Pain[2]" [reference 1 below] which favorably compares Ciprodex to Cortisporin. Finally, on page four of the aid, in the chart discussed above, the chart specifically favorably compares Ciprodex to Cortisporin with respect to pain relief in the "Less Pain by Day Two" category.

These claims state that Ciprodex provides faster pain relief than Cortisporin and that more patients experience less pain with Ciprodex, when this has not been demonstrated by substantial evidence. The references[1, 2] cited are insufficient to support these claims because the specific comparison claimed between the Ciprodex treatment group and Cortisporin treatment group was not a pre-specified endpoint in the study. Of the 42 comparisons made between Ciprodex and Cortisporin, only two cases were nominal p-values. Any appropriate corrections made for multiple comparisons would show that these comparisons are not statistically significant.

Third, the sales aid presents false or misleading claims regarding the superiority of Ciprodex over Cortisporin with respect to the reduction of inflammation. Page two of the aid states:

- "You're sunk without a more efficient anti-inflammatory."
- "CIPRODEX® Otic, with the powerful anti-inflammatory dexamethasone, was significantly more effective in reducing inflammation than CORTISPORIN Otic[4]" [reference 3 below]

Similarly, on page four, Ciprodex is designated as the "More Effective Anti-inflammatory" in the chart entitled "Proven Results in Otitis Externa."

These claims and presentations are false or misleading because they state that Ciprodex is more effective in reducing inflammation than Cortisporin, when this has not been demonstrated by substantial evidence. In the study cited, Roland et al.,[3] Ciprodex did not demonstrate a significant difference in inflammation at three of the four time points studied (days one, three, and eight); the only significant difference was seen at day 18. There is no analysis making appropriate corrections for the multiple endpoints and no clear intent in the protocol to conduct this analysis. Therefore, the data do not support the above claims of superior anti-inflammatory activity for Ciprodex.

Fourth, the sales aid makes false or misleading claims and presentations when comparing the treatment failure rates of the two drugs. On page three, the aid states:

- "Twice the treatment success makes quite a splash."
- "In a comparison against the most common otitis externa pathogen-*Pseudomonas aeruginosa*- CORTISPORIN* Otic had more than two times the treatment failure rate of CIPRODEX® Otic[4]" [reference 3 below]

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[1] Roland PS, Block SL, Latiolais TG, et al. A comparison of ciprofloxacin/dexamethasone and neomycin/polymyxin B/hydrocortisone for the treatment of acute otitis externa [abstract]. *ASPO*, January 31, 2005.

[2] Data on file, Alcon Laboratories, Inc. (C98-18)

[3] Roland PS, Pien FD, Schultz CC, et al. Efficacy and safety of topical ciprofloxacin/dexamethasone versus neomycin/polymyxin B/hydrocortisone for otitis externa. *Curr Med Res Opin* 2004; 20:1175-1183.

Page three also contains a graph entitled "Fewer Treatment Failures in Otitis Externa[4]" [reference 3 on the previous page] which presents Ciprodex favorably when compared to Cortisporin, as does the chart on page four of the aid in the category labeled "More Successful Treatments."

These claims are false or misleading because they imply that Ciprodex has a lower rate of treatment failures relative to Cortisporin, when this has not been demonstrated by substantial evidence or substantial clinical experience. The claimed advantage is not based on a pre-specified analysis and is not consistent across studies. When evaluating for differences between treatment groups, the study must be designed to look for these differences prospectively.

Finally, the sales aid makes false or misleading claims or presentations regarding the superiority of Ciprodex over Cortisporin when comparing the risk profile of both products. The third page of the aid is entitled "Right in Your Backyard: Greater Safety and Success" and goes on to state:

- "1 out of 8 patients had an allergic reaction to neomycin, an active ingredient in CORTISPORIN Otic[8]" [reference 4 below]

The sales aid exaggerates the risk of allergic reactions to neomycin, an active ingredient in Cortisporin. The reference[4] cited was a test performed on subjects with chronic eczema of the outer ear canal or recurrent external otitis. The test performed was a provocative test intended to elicit delayed hypersensitivity reactions. Patch testing was performed on stripped skin using allergens prepared as pastes. They were applied to stripped skin on inert metal discs for 48 hours, and erythema and induration were measured upon disc removal and 24 hours later. These experimental conditions do not mimic the clinical usage of topical otic antimicrobials, and the reported results grossly exaggerate the incidence of allergic reactions to neomycin.

Omission of Material Fact – Sales Aid

As described above, the third page of the sales aid contains claims and presentations regarding the risks of allergic reactions associated with an ingredient of Cortisporin. However, these presentations misleadingly fail to reveal a Warning associated with Ciprodex that is material in light of these representations. Specifically, the Warnings section of Ciprodex's PI states that Ciprodex "should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have occurred in patients receiving systemic quinolones. Serious acute hypersensitivity reactions may require immediate emergency treatment."

Conclusion and Requested Actions

Your sales aid and retail sell sheet omit material facts about Ciprodex, including important risks associated with the use of Ciprodex and important limitations to its indication. Moreover, your sales aid makes numerous unsubstantiated superiority claims. Thus, these materials misbrand your drug in violation of the Act, 21 U.S.C. §§352(a) and 321(n).

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[4] Schapowal AG. Contact dermatitis to antibiotic ear drops is due to neomycin but not to ciprofloxacin. Presented at the XXth Congress of the European Academy of Allergology and Clinical Immunology; May 2001, Berlin, Germany.

DDMAC requests that Alcon immediately cease the dissemination of violative promotional materials for Ciprodex such as those described above. Please submit a written response to this letter on or before May 4, 2007 stating whether you intend to comply with this request, listing all violative promotional materials for Ciprodex that are 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, facsimile at 301-796-9877. In all future correspondence regarding this particular matter please refer to the MACMIS ID # 13836 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 Ciprodex 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

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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