DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Seane D. Jones, M.S., R.A.C.
Assistant Director, Regulatory Affairs
Alcon Research, Ltd.
6201 South Freeway
Fort Worth, TX 76134-2099

RE: Cipro HC Otic Suspension (Ciprofloxacin Hydrochloride and Hydrocortisone Otic Suspension)
NDA 20-805

Ciloxan (ciprofloxacin ophthalmic) Solution
NDA 19-992

MACMIS ID# 11015

Dear Ms. Jones:

This letter notifies Alcon Research, Ltd. (Alcon) that through routine monitoring and surveillance, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified activities and promotional materials for Cipro HC Otic Suspension and Ciloxan Ophthalmic Solution that are in violation of the Federal Food, Drug, and Cosmetic Act and its implementing regulations. The promotional materials are identified as sales aids CHC02500VS, CHC02504VS, CHC02508VS, and CHC02509VS. The promotional materials make false or misleading claims regarding the efficacy and safety profiles of each of your drugs. In addition, your sales representatives have promoted each drug for uses that have not been proven safe and effective by substantial evidence or substantial clinical experience.

Specifically, DDMAC objects to the following:

Print Materials

Omission and Minimization of Risk Information

Promotional materials are false or misleading if they fail to reveal facts material in light of representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. (See 21 CFR § 202.1(c)(5)(iii)) Your claims promoting a lack of allergic reactions are especially troublesome because they contradict the Warnings section of the PI and omit important contextual information regarding this Warning. Specifically, you fail to present the following important risk information for Cipro HC Otic from the Warnings section of the approved product labeling (PI):

- Warnings - Cipro HC 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.

In addition, the sales aids are misleading because they fail to note the Contraindication that Cipro HC Otic is a nonsterile product, an important consideration in understanding its indicated use. Use of a nonsterile product in patients with non-intact tympanic membranes can result in the introduction of contaminating microorganisms into the middle ear spaces and consequently result in a middle ear infection. Although the sales aids note that the product is contraindicated in persons with nonintact tympanic membranes, they fail to provide the necessary context that this is because the product is nonsterile. Because the Contraindications and Warnings statements in the PI regarding hypersensitivity are directed at different populations, it is important to include both.

Furthermore, you fail to present important risk information for Cipro HC Otic, namely, the following Precaution contained in the PI:

- Precautions General - If the infection is not improved after one week of therapy, cultures should be obtained to guide further treatment.

The failure to present this important risk information may lead to serious health risks because failure to improve may represent a fungal superinfection or a resistant bacterial infection.

Promotional materials may be false or misleading if they fail to present information relating to side effects and contraindications of a drug with a prominence and readability reasonably comparable with the presentation of information relating to effectiveness of the drug. (See 21 CFR § 202.1(e)(7)(viii)) Specifically, the sales aids present large, prominent claims and representations concerning Cipro HC Otic's effectiveness over several pages, including but not limited to, "YOU DON'T WANT 19 EXTRA HOURS OF THIS … OR OF OTITIS EXTERNA. ONLY CIPRO HC OTIC ENDS THE PAIN 19 HOURS SOONER." In contrast, the risk information that you present is on the bottom of the last page of the sales aids in a single-spaced paragraph in small point-size with no additional emphasis. Important information about contraindications and most frequent adverse events is presented in the middle of the paragraph, in between the indication statement and the instructions for the sales representative to provide prescribing information. Therefore, your sales aid is misleading because it minimizes important risk information associated with Cipro HC Otic therapy.

Unsubstantiated Superiority Claims – Efficacy

Promotional materials are false or misleading if they contain a drug comparison that represents or suggests that a prescription drug is more effective than another drug when such has not been demonstrated by substantial evidence or substantial clinical experience. (See 21 CFR § 202.1(e)(6)(ii)) The primary theme of the promotional materials, cited above, is that Cipro HC Otic provides faster relief of the pain associated with acute otitis externa than other available treatment options. For example, on the first page of sales aid CHC02500VS, the claim "YOU DON'T WANT 19 EXTRA HOURS OF THIS" prominently appears in large, white, block letters against a bright orange

background. The sales aid opens up to a two-page spread featuring a photograph of two young boys screaming and running away from UFOs. Under this photograph, the claim from page one of the sales aid continues in large, white, block letters, " … OR OF OTITIS EXTERNA. ONLY CIPRO HC OTIC ENDS THE PAIN 19 HOURS SOONER." Adjacent to this claim is the tag line, "What a difference a day makes." These claims suggest that Cipro HC Otic is superior to other available treatment options for the treatment of acute otitis externa because it is the only treatment option that ends ear pain 19 hours sooner. We note that you have listed a clinical trial, conducted by Pistorius et al.[1], in support of these claims. However, this trial is inadequate to support your claims for the following reasons.

First, the trial did not compare Cipro HC Otic to all available treatment options, as the claims suggest. Specifically, it is a three-arm comparative trial that compared Cipro HC Otic with two other treatments: an investigational otic preparation of ciprofloxacin alone and an otic suspension of polymyxin B-neomycin-hydrocortisone (Cortisporin – Monarch Pharms). Second, therapy with Cipro HC Otic resulted in a median time to end of ear pain of 3.79 days (91 hours). This outcome was not significantly different from patients treated with polymyxin B-neomycin-hydrocortisone who experienced a median time to end of ear pain of 4.07 days (98 hours). Therefore, to the extent your claim that "Only Cipro HC Otic ends ear pain 19 hours sooner" is based on the cited trial, your claim is misleading because Cipro HC Otic has not been demonstrated through prospective, well-developed, adequately controlled clinical trials to end ear pain 19 hours sooner than all available treatment options. FDA is not aware of any studies to support these claims.

You present additional unsubstantiated superiority claims in sales aid CHC02504VS. For example, you present the headline, "Dramatic results from an unbeatable combination," in conjunction with the following bulleted claims:

- Hydrocortisone accelerates total pain relief
- Cipro HC Otic ends ear pain 19.2 hours faster – almost a full day sooner – than a fluoroquinolone with no steroid (p=0.036)

This presentation suggests that Cipro HC Otic is superior to a fluoroquinolone without a steroid because it ends ear pain 19.2 hours faster. However, the clinical trial cited (Pistorius et al.) only demonstrated that Cipro HC Otic ended ear pain faster than an investigational otic preparation of ciprofloxacin alone. This preparation has not been proven to be safe or effective for the treatment of otitis externa. Therefore, this presentation is misleading.

Unsubstantiated Superiority Claims –Safety

Promotional materials are false or misleading if they contain a drug comparison that represents or suggests that a prescription drug is safer than another drug when such has not been demonstrated by substantial evidence or substantial clinical experience. (See 21 CFR § 202.1(e)(6)(ii)) Specifically, the sales aids present claims that state or suggest that Cipro HC Otic is safer than neomycin and aminoglycosides for the treatment of acute otitis externa. For example, you present the following claims:

[1] Pistorius B, Westberry K, Drehobl M, et al. Prospective, randomized, comparative trial of ciprofloxacin otic drops, with or without hydrocortisone, vs. polymyxin B-neomycin-hydrocortisone otic suspension in the treatment of acute diffuse otitis externa. *Infect Dis in Clin Pract*. 1999;8:387-395.

- "**Cipro HC Otic is safer than aminoglycosides** – Cortisporin showed greater toxicity than any of the fluoroquinolones tested." CHC02504VS
- "In testing of cochlear outer hair cells, cells in the Cipro HC Otic group survived three times as long as cells in the aminoglycoside group." CHC02500VS

These claims are misleading because they are based on an *in vitro* study[2] of several topical otic preparations on isolated chinchilla cochlear outer hair cells. Such data are not an adequate basis on which to make conclusions about clinical safety. (See 21 CFR § 202.1(e)(6)(vii)) FDA is not aware of any *in vivo* studies to support these claims.

Similarly, you present the headline "Greater Safety Profile" in conjunction with the following bulleted claims in sales aids CHC02500VS, CHC02504VS, and CHC02508VS:

- "Unlike neomycin, Cipro HC Otic does not induce allergic reactions."
- "Topical allergic reaction rates following patch testing: 13% neomycin sulfate, 0% CIPRO HC Otic."

These claims misleadingly suggest that Cipro HC Otic has been demonstrated to be safer, or have fewer side effects, than neomycin sulfate. However, we are not aware of any adequate, well-controlled, head-to-head clinical trials specifically designed to assess the safety of Cipro HC Otic as compared to neomycin sulfate. We note that in support of these claims you have listed an abstract of an open-label study enrolling 62 patients presented at the XXth Congress of the European Academy of Allergology and Clinical Immunology by Schapowal et al.[3] However, this study does not provide substantial evidence to support these claims. Specifically, open-label studies can cause bias when evaluating study subjects. In addition, this study was based on only 62 patients and the statistical power is insufficient to detect differences between treatment groups.

Overstatement of Efficacy

Promotional materials are false or misleading if they represent or suggest that a prescription drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience. (See 21 CFR § 202.1(e)(6)(i)) Specifically, in sales aid CHC02504VS, you claim, "In clinical studies, Cipro HC Otic killed 98% of *P.aeruginosa* and 94% of *S.aureus*," and you reference the clinical trial conducted by Pistorius B. et al. This claim is misleading because it selectively presents data in a way that overstates the clinical efficacy shown in this trial. First, this claim overstates the efficacy of Cipro HC Otic by suggesting a higher per pathogen eradication rate than what is supported by substantial evidence. Specifically, this outcome fails to include patients with indeterminate and missing responses. When these patients are included, the per pathogen eradication rates are 89.8% for *P.aeruginosa* and 88.9% for *S.aureus*. Second, in the absence of contextual information regarding clinical success rates, this presentation of the microbiological responses suggests that the bacteriologic eradication rate is equivalent to clinical success at the end of therapy (i.e., 98% and 94% clinical

[2] Russell PT, Church CA, Jinn TH, et al. Effects of common topical otic preparations on the morphology of isolated cochlear outer hair cells. *Acta Otolaryngol*. 2001; 121:135-139.
[3] 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.

success rate). However, in the study cited, the clinical response at the end of therapy (resolution or improved) was 90% for Cipro HC Otic. Notably, this clinical response rate is not presented in your sales aid. Therefore, this claim overstates the efficacy of Cipro HC Otic by suggesting a higher rate of clinical response than has been demonstrated by substantial evidence or substantial clinical experience.

In sales aid CHC02508VS, you claim that "*In vitro*, Cipro HC Otic kills 99.9% of *P.aeruginosa* pathogens in just 15 minutes or less." You reference data on file to support this claim. The data on file are contained in technical report number 098:38540:1295 titled*, "In vitro* kinetics of kill of gram-positive bacterial species by Ciloxan and Ocuflox." This study did not examine the effects of Cipro HC Otic on *P.aeruginosa* but instead utilized the drug products Ciloxan and Ocuflox. Therefore, to the extent that your claim that "Cipro HC Otic kills 99.9% of *P.aeruginosa* pathogens in just 15 minutes or less" is based on the technical report, the claim is false or misleading.

Unsubstantiated Claims

Promotional materials are false or misleading if they contain claims that a drug is better than has been demonstrated by substantial evidence or substantial clinical experience. (See 21 CFR 202.1(e)(6)(i)) In particular, sales aid CHC02509VS claims that "Cipro HC Otic takes the pain out of compliance." This claim appears above a chart comparing the dosing and administration of Cipro HC Otic to Floxin Otic and Corticosporin. This claim, presented in conjunction with the chart, implies that characteristics of the Cipro HC Otic product and its dosage and administration cause patients to experience higher compliance rates compared to Floxin Otic and Cortisporin. FDA is not aware of any such characteristic; neither is FDA aware of any evidence supporting higher rates of compliance for Cipro HC Otic over Floxin Otic and Corticosporin. In fact, you cite no data to support this claim. Even though Cipro HC Otic requires fewer drops for a full course of therapy than the comparator products in the chart, FDA is not persuaded that 6 versus 10 drops per day makes a difference in patient compliance. Nor is FDA aware of any evidence to support the suggestion that the comparison between product inserts concerning the number of minutes necessary for adequate drop penetration is clinically significant. Furthermore, compliance (i.e., patient adherence to treatment regimen) is influenced by more than convenience of dosing. Other factors, such as adverse effects of Cipro HC Otic and its comparators, must also be considered. Therefore, this claim of higher rates of compliance for Cipro HC Otic versus Floxin Otic and Cortisporin is misleading without substantial evidence.

In sales aids CHC02508VS, and CHC02509VS, you present the prominent headers "Combination strength ends the pain sooner" and "Only Cipro HC Otic ends the pain 19 hours sooner," respectively. In conjunction with these prominent headers appears the bulleted claim, "OE [otitis externa] pain is severe – over one third of patients have their daily lives interrupted; 1 out of 5 requires bed rest" and references the study by Van Asperen et al.[4] This presentation suggests that because Cipro HC Otic ends the pain sooner, treatment with Cipro HC Otic will also have an effect on the "interruption of patients daily lives," specifically the requirement of bed rest. Such claims of treatment benefit require substantial evidence as demonstrated through adequate and well-controlled prospective trials utilizing well-developed and validated measures. However, the reference cited in your sales aid fails to provide substantial evidence to support this claim. Indeed, because the particular types of treatment were not discussed it is not known if Cipro HC Otic was used by the patients in the study. The cited reference is

[4] Van Asperen IA, de Rover CM, Schijven JF, et al. Risk of otitis externa after swimming in recreational fresh water lakes containing Pseudomonas aeruginosa. *BMJ*. 1995;311:1407-1410.

a retrospective, epidemiological investigation of an outbreak of acute otitis externa that is not representative of the general population affected by otitis externa, which generally occurs sporadically. The objective of the study was to determine whether an outbreak of otitis externa was due to bathing in recreational fresh water lakes and to establish whether the outbreak was caused by Pseudomonas aeruginosa in the water. The study was not designed to measure Cipro HC Otic's impact on treatment outcomes such as bed rest. Therefore, this presentation, suggesting that treatment with Cipro HC Otic can help patients resume their daily lives or not require bed rest, is misleading because it is not supported by substantial evidence or substantial clinical experience.

Oral Representations Promoting Cipro HC Otic

The Indications and Usage section of the PI for Cipro HC Otic states that, "Cipro HC Otic is indicated for the treatment of **acute otitis externa** in adult and pediatric patients, one year and older, due to susceptible strains of *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Proteus mirabilis* (emphasis added)." In addition, the Contraindications section of the PI for Cipro HC Otic states that, "This nonsterile product should not be used if the tympanic membrane is perforated." Notwithstanding Cipro HC Otic's approved indication and contraindication, your sales representatives have promoted Cipro HC Otic to health care practitioners for the treatment of patients with perforated tympanic membranes. Your sales representatives also promoted Cipro HC Otic for the treatment of acute otitis media in pediatric patients with tympanostomy tubes that perforate the tympanic membrane. For example, your sales representatives made the following promotional statements regarding Cipro HC Otic to health care practitioners:

- Cipro HC Otic can be safely used in patients with a perforated tympanic membrane and patients with tympanostomy tubes.
    - It's an anti-inflammatory. Isn't that what you need, doctor? The medicine gets in there [perforated tympanic membrane] at a higher concentration.
- Cipro HC Otic is safe and is considered to be the standard of care for kids with tympanostomy tubes.
- Other ENTs recommend Cipro HC Otic first-line for all kids with tubes.
- You aren't practicing the standard of care if you aren't using Cipro HC Otic for this use [in patients with tympanostomy tubes].

These statements are particularly concerning from a patient health perspective because, as previously stated, the use of a nonsterile product in patients with non-intact tympanic membranes can result in the introduction of contaminating microorganisms into the middle ear spaces and consequently result in a middle ear infection.

Further examples of oral statements made by your sales representatives include the claim, "Cipro HC Otic is more effective than Floxin[5]." FDA is not aware of any studies comparing Cipro HC Otic[6] to Floxin Otic (ofloxacin otic solution) 0.3% (Daiichi Pharmaceutical Corp). Furthermore,

[5] Floxin Otic (ofloxacin otic solution) 0.3% is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below:
Otitis Externa in adults and pediatric patients, one year and older, due to *Staphylococcus aureus* and *Pseudomonas aeruginosa.*

because you compare the effectiveness of two products that have dissimilar indications, this claim promotes the use of Cipro HC Otic for a use that is contraindicated. Specifically, Floxin is indicated for a broader range of conditions than Cipro HC Otic, including acute otitis media in pediatric patients one year and older with tympanostomy tubes and chronic suppurative otitis media in patients 12 years and older with perforated tympanic membranes. As previously stated, Cipro HC Otic is contraindicated for patients with perforated tympanic membranes.

Oral Representations Promoting Ciloxan

Your sales representatives have also promoted Ciloxan[7] (ciprofloxacin opthalmic) Solution for unapproved new uses for which FDA is not aware of any clinical studies. Ciloxan ophthalmic solution is indicated for the treatment of infections caused by specific microorganisms in the conditions of corneal ulcers and conjunctivitis. However, your sales representatives have made claims such as, "Ciloxan is safe and effective for the treatment of otitis media and otitis externa." These representations suggest that Ciloxan is useful in a broader range of patients or conditions than has been demonstrated by substantial evidence or substantial clinical experience. FDA is not aware of any clinical studies to support these claims.

Requested Actions

Alcon should immediately discontinue the above promotional activities and promotional materials for Cipro HC Otic and Ciloxan that contain the same or similar presentations. We request that Alcon respond in writing with its intent to discontinue such activities and use. Please respond in writing to us within ten business days of the date of this letter. Your response should list similarly violative materials with a description of the method for discontinuation and the discontinuation date.

Chronic Suppurative Otitis Media in patients 12 years and older with perforated tympanic membranes due to *Staphylococcus aureus, Proteus mirabilis, and Pseudomonas aeruginosa* .
Acute Otitis Media in pediatric patients one year and older with tympanostomy tubes due to *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and *Pseudomonas aeruginosa* .

[6] Cipro HC Otic (ciprofloxacin HCl and hydrocortisone otic suspension) is indicated for the treatment of acute otitis externa in adult and pediatric patients, one year and older, due to susceptible strains of *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Proteus mirabilis*.

[7] Ciloxan (ciprofloxacin HCl) Ophthalmic solution is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below:
Corneal Ulcers—*Pseudomonas aeruginosa, Serratia marcescens, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneomoniae, Streptococcus* (Viridans Group);
Conjunctivitis—*Haemophilus influenzae, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneomoniae.*

Your response should be directed to the undersigned by facsimile at (301) 594-6771, or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42, Room 8B-45, 5600 Fishers Lane, Rockville, MD 20857.

In all future correspondence regarding this matter, please refer to MACMIS ID #11015 in addition to the NDA number. DDMAC reminds Alcon that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Sonny Saini, Pharm.D.
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/

Sonny Saini

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