DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993-0002

TRANSMITTED BY FACSIMILE

David R. Bethune
Chief Executive Officer
Zila Pharmaceuticals, Inc.
5227 North 7th Street
Phoenix, AZ 85014-2800

RE: NDA # 19-028
Peridex® (chlorhexidine gluconate 0.12%) Oral Rinse
MACMIS ID # 16307

WARNING LETTER

Dear Mr. Bethune:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a professional mailer (ZILA-48-2007) for Peridex® (chlorhexidine gluconate 0.12%) Oral Rinse (Peridex) submitted by Zila, Inc. (Zila) under cover of Form FDA-2253. The professional mailer includes a letter, brochure, and the approved product labeling (PI) for Peridex. The promotional pieces in the mailer are false or misleading because they present efficacy claims for Peridex but fail to communicate **any** information about the risks associated with its use, make unsubstantiated superiority claims, fail to use the required established name,
overstate the efficacy and omit material facts, and broaden the indication. Moreover, these promotional materials make false or misleading representations about a competitive product. Thus, your professional mailer misbrands Peridex in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(a) & 321(n), and FDA implementing regulations. 21 CFR 201.6(a) & 201.10(g)(1). *Cf.* 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i); (e)(6)(ii) & (e)(6)(x).

Background

According to the PI:

> Peridex Oral Rinse is indicated for use between dental visits as part of a professional program for the treatment of gingivitis as characterized by redness and swelling of the gingivae, including gingival bleeding upon probing. Peridex Oral Rinse has not been tested among patients with acute necrotizing ulcerative gingivitis (ANUG). For patients having coexisting gingivitis and periodontitis, see PRECAUTIONS.

The PI includes the following risk information, in pertinent part:

CONTRAINDICATIONS: Peridex Oral Rinse should not be used by persons who are known to be hypersensitive to chlorhexidine gluconate or other formula ingredients.

WARNINGS: The effect of Peridex Oral Rinse on periodontitis has not been determined. An increase in supragingival calculus was noted in clinical testing in Peridex Oral Rinse users compared with control users. It is not known if Peridex Oral Rinse use results in an increase in subgingival calculus. Calculus deposits should be removed by a dental prophylaxis at intervals not greater than six months. Hypersensitivity and generalized allergic reactions have occurred.

PRECAUTIONS:
GENERAL:

1. For patients having coexisting gingivitis and periodontitis, the presence or absence of gingival inflammation following treatment with Peridex Oral Rinse should not be used as a major indicator of underlying periodontitis.
2. Peridex Oral Rinse can cause staining of oral surfaces, such as tooth surfaces, restorations, and the dorsum of the tongue. Not all patients will experience a visually significant increase in toothstaining. In clinical testing, 56% of Peridex Oral Rinse users exhibited a measurable increase in facial anterior stain, compared to 35% of control users after six months; 15% of Peridex Oral Rinse users developed what was judged to be heavy stain, compared to 1% of control users after six months. Stain will be more pronounced in patients who have heavier accumulations of unremoved plaque. Stain resulting from use of Peridex Oral Rinse does not adversely affect health of the gingivae or other oral tissues. Stain can be removed from most tooth surfaces by conventional professional prophylactic techniques.
   Additional time may be required to complete the prophylaxis. Discretion should be used when prescribing to patients with anterior facial restorations with rough surfaces or margins. If natural stain cannot be removed from these surfaces by a dental prophylaxis, patients should be excluded from Peridex Oral Rinse treatment if permanent discoloration is unacceptable. Stain in these areas may be difficult to remove by dental prophylaxis and on rare occasions may necessitate replacement of these restorations.
3. Some patients may experience an alteration in taste perception while undergoing treatment with Peridex Oral Rinse. Rare instances of permanent taste alteration following Peridex Oral Rinse use have been reported via post-marketing product surveillance.

PEDIATRIC USE: Clinical effectiveness and safety of Peridex Oral Rinse have not been established in children under the age of 18.

ADVERSE REACTIONS: The most common side effects associated with chlorhexidine gluconate oral rinses are: 1) an increase in staining of teeth and other oral surfaces; 2) an increase in calculus formation; and 3) an alteration in taste perception; see WARNINGS and PRECAUTIONS. Oral irritation and local allergy-type symptoms have been spontaneously reported as side effects associated with use of chlorhexidine gluconate rinse.

Omission 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. Both the letter and brochure provided in the professional mailer make numerous efficacy claims for Peridex, including claims that it is "the gold standard in gingivitis treatment," an "ideal solution for your growing dental practice," and "a proven way to combat gingivitis." However, these promotional materials entirely omit risk information for Peridex, including the contraindication, warnings, precautions, and most frequently reported adverse events from the PI. We note that the PI is included in the envelope along with the letter and brochure, but the inclusion of the PI is not sufficient to provide appropriate qualification or pertinent information for the claims made in the letter and brochure. For pieces to be non-misleading, they must contain risk information in each part as necessary to qualify any safety or effectiveness claims made. *Cf.* 21 CFR 202.1(e)(3)(i).

Misleading Superiority Claims and Failure to Use Required Established Name

The letter accompanying the brochure claims, "**What if** you ordered a **Cadillac** but they **delivered a Yugo?** That's like **prescribing** PERIDEX,® and the pharmacist **substituting** a **generic**" (original emphasis). The letter continues (original emphasis):

> Here's the scenario: Your patient needs the **proven power of PERIDEX.** You write down a prescription for the **brand** that's been the **gold standard** in gingivitis treatment since it created the chlorhexidine rinse category. The patient goes to the pharmacy, secure in the knowledge that you've got his or her best interests in mind, and that's when things go awry. The pharmacist substitutes a generic—and your patient gets something **that really isn't PERIDEX**. To date, there have been no published efficacy studies between the brand PERIDEX and any generic rinses.

Similarly, the brochure states (original emphasis):

- **What if** you ordered a **Cadillac** but they **delivered a Yugo**? That's similar to prescribing PERIDEX® and a pharmacist giving your patient anything *but* the brand that started it all. We'll help you avoid the switch…"
- **Give your patients what they deserve. PERIDEX.**
- [H]elp them battle gingivitis with the brand that is the acknowledged gold standard in chlorhexidine rinses
- [A]void the generic substitutions at the pharmacy that undermine your authority and weaken your relationship with patients

These claims suggest that Peridex is the gold standard for chlorhexidine gluconate 0.12% solutions; that it is superior to other chlorhexidine gluconate 0.12% solutions; and that no other solution is equivalent to or useful in place of Peridex. However, FDA has reviewed and approved a number of therapeutically equivalent formulations of chlorhexidine gluconate 0.12% solution since 1995. These products were granted an "AT" rating. This rating means that the Agency considers the products therapeutically equivalent; one can be substituted for the other with the full expectation that the substituted product will produce the same clinical effect and

safety profile as the prescribed product.[1] Unless and until the Agency's determination is changed or reversed, any promotion suggesting a lack of equivalence between Peridex and products deemed to be its therapeutic equivalent are considered false or misleading. These claims are particularly disturbing in light of the fact that neither the letter nor the brochure presents the full established name of Peridex, despite the requirement to do so. See 21 CFR 201.10(g)(1).

Overstatement of Efficacy/Omission of Material Facts

Promotional materials are misleading if they contain representations that the drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience. The letter and brochure claim, among other things (emphasis original):

- [I]t's clinically proven to last up to 12 hours and can **kill up to 97%** of aerobic and anaerobic bacteria[2]
- PERIDEX lasts up to 12 hours and can kill up to 97% of aerobic and anaerobic bacteria
- [T]he 12-hour bacteria fighting power of PERIDEX….

These claims as to the effectiveness of Peridex in the oral cavity are misleading because they are not supported by substantial evidence or substantial clinical experience. The PI, which you cite in support of these claims, is silent on when significant levels of Peridex disappear after a patient has used this product as directed (i.e., swish 15 ml undiluted for 30 seconds, then spit out) and provides no support for a 12-hour duration of antibacterial effect. The PI states that there is no chlorhexidine in plasma at 12 hours, and that statement neither addresses when, or indeed whether, chlorhexidine was present in plasma, nor does it say anything about the relevance of plasma levels given the topical effect of chlorhexidine. If you have evidence to support the 12 hour antibacterial claim, please submit it to the Agency for review.

We also note that two of the above claims selectively present only the uppermost bound, i.e., up to 97%, of a wide ranging value for percentage of bacterial reduction, and omit important information regarding the actual bacteria assayed. As stated in the PI, "[m]icrobiological sampling of plaque has shown a general reduction of counts of **certain assayed bacteria**, both aerobic and anaerobic, ranging from **54**-97% through six months use" (emphasis added). Finally, you have failed to provide the important material information from the PI that states, "The clinical significance of Peridex Oral Rinse's antimicrobial activities is not clear." This selective presentation of information is misleading.

Broadening of Indication

The brochure claims (emphasis original):

> **Protect their overall health.** Mounting evidence has linked diseases of the mouth with other serious medical conditions, including heart disease, stroke, uncontrolled diabetes, low preterm births, and respiratory disease. Protecting your patients' oral health is about

[1] Electronic Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations, current through December 31, 2006. Available at http://www.fda.gov/cder/ob/default.htm (last accessed January 2, 2008).
[2] Reference to PI.

> more than just smiles—and a regimen of PERIDEX applications can put your patients on the road to good oral health—which, in turn, can improve their overall health. That's why it's vital to begin a PERIDEX dispensing program now.

This claim states that a regimen of Peridex can lead to good oral health and that good oral health can, in turn, improve patients' health with specific reference to serious medical conditions, including heart disease, stroke, uncontrolled diabetes, low preterm births, and respiratory disease. There is no evidence that Peridex has such effects with regard to overall health or serious medical conditions, including heart disease, stroke, uncontrolled diabetes, low preterm births, and respiratory disease. As the PI indicates, Peridex is indicated for use between dental visits for the treatment of gingivitis.

The letter claims:

- Up to 80% of your patients might suffer from gingivitis – which left untreated can lead to more destructive forms of periodontal disease, such as periodontitis. Get your patients started on PERIDEX therapy during the early stages of gingivitis….when the disease is reversible with professional treatment and good, at-home oral hygiene practices.
- …**help them heal.**

These claims imply that treatment with Peridex, along with good oral hygiene practices, can ***cure*** or ***heal*** gingivitis by reversing the condition and preventing it from progressing to more destructive forms of periodontal disease. In fact, Peridex is only indicated as part of a professional program for the ***treatment*** of gingivitis. FDA is not aware of evidence that Peridex can *heal* gingivitis and prevent other forms or periodontal disease.

Furthermore, these claims misleadingly broaden the indication for Peridex by implying that <u>all</u> patients with gingivitis are candidates for Peridex therapy when, as stated in the PI, the safety and effectiveness of Peridex has not been established in patients under the age of 18. Both pieces fail to reveal this material information. Thus, these pieces misleadingly suggest that Peridex is useful in a broader range of patients and conditions than has been demonstrated by substantial evidence or substantial clinical experience.

Conclusion and Requested Action

For the reasons discussed above, your professional mailer misbrands Peridex in violation of the Act, and FDA's implementing regulations. 21 U.S.C. 352(a) & 321(n); 21 CFR 201.6(a) & 201.10(g)(1). *Cf.* 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i); (e)(6)(ii) & (e)(6)(x).

DDMAC requests that Zila immediately cease the dissemination of violative promotional materials for Peridex such as those described above. Please submit a written response to this letter on or before May 2, 2008, stating whether you intend to comply with this request, listing all violative promotional materials for Peridex 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, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to the MACMIS #16307 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 Peridex 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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