DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-753/S-002

Chiron Corporation
Attention: William H. Pitlick, Ph.D.
Vice President, Regulatory Affairs
4560 Horton Street
Emerville, CA 94608-2916

Dear Dr. Pitlick:

Please refer to your supplemental new drug application dated July 29, 1999, received July 30, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TOBI ®(tobramycin solution for inhalation). We note that this application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated August 5, and August 20, 1999.

This supplemental new drug application provides for revisions to the "**WARNINGS: Ototoxicity**", "**PRECAUTIONS** : ***Safety Information***", and "**PRECAUTIONS**: ***Audiograms***" sections of the package insert.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the labeling submitted on July 29, 1999, and with the agreed upon labeling for the **WARNINGS**: **Ototoxicity** section as listed below.

> "Ototoxicity, as measured by complaints of hearing loss or by audiometric evaluations, did not occur with TOBI therapy during clinical studies. However, transient tinnitus occurred in eight TOBI-treated patients versus no placebo patients in the clinical studies. Tinnitus may be a sentinel symptom of ototoxicity, and therefore the onset of this symptom warrants caution (see **ADVERSE REACTIONS**). Ototoxicity, manifested as both auditory and vestibular toxicity, has been reported with parenteral aminoglycosides. Vestibular toxicity may be manifested by vertigo, ataxia or dizziness.
> **In postmarketing experience, patients receiving TOBI have reported hearing loss.** Some of these reports occurred in patients with previous or concomitant treatment with systemic aminoglycosides. Patients with hearing loss frequently reported tinnitus."

Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the text for the package insert submitted on July 29, 1999, and include the revision listed above. Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 50-753/S-002." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Judit Milstein, Regulatory Project Manager, at (301) 827-2207.

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Janice Soreth

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