

CHIRON

Chiron Corporation
4560 Horton Street
Emeryville, California 94608-2916
510.655.8730

20 April 2004

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, Maryland 20852

**RE: Docket 2004P-0131 - Comments on ANDA Suitability Petition for TOFIN™
(tobramycin solution for inhalation)**

Dear Sir or Madam:

I am submitting the following comments on behalf of Chiron Corporation in response to the SourceCF suitability petition requesting permission to file an Abbreviated New Drug Application (ANDA) for TOFIN™ (tobramycin solution for inhalation). The petition requests a change in product concentration, volume, total drug content and formulation, and also proposes administration of the new drug product via a delivery system that is unapproved or uncleared as well as different from the delivery system in the approved labeling of the reference listed drug. The reference listed drug is TOBI® (tobramycin solution for inhalation), which is manufactured by Chiron Corporation under New Drug Application (NDA) No. 50-753.

The Petition should be denied because the proposed changes in drug concentration, volume and formulation clearly raise serious questions of safety and effectiveness and require that animal and clinical investigations be conducted to assure the proposed drug product is safe and effective. The proposed changes would also require significant changes to the approved TOBI labeling to address novel safety issues. The higher drug concentration and volume combined with the likelihood of administration with currently marketed nebulizers would create heightened risks of product overdose with attendant increases in patient adverse events, including but not limited to hearing loss. The Petition proposes use of an unapproved or uncleared delivery system with the proposed drug product, a type of product change not authorized by section 505(j)(2)(C) of the Food, Drug and Cosmetic Act (FDCA) for approval under a Suitability Petition. The Petition also seeks permission to file an ANDA for a combination product which, under the FDCA, requires submission of a New Drug Application (NDA).

Background

TOBI® is approved by the Food and Drug Administration (FDA) for the treatment of cystic fibrosis patients with *Pseudomonas aeruginosa* infection. In the pivotal TOBI clinical

2004P-0131

C 1

trials involving approximately 500 cystic fibrosis patients, lung function improved by as much as 11 percent compared to controls during six months of treatment, and hospital admissions decreased by 26 percent. Because of its important potential to address unmet medical needs in the treatment of a serious and life-threatening illness, TOBI was approved by FDA on December 22, 1997 under fast track authority in 5 months and 12 days. TOBI also received an orphan product designation from FDA on June 18, 1999, and was granted seven years of orphan exclusivity upon its approval for the treatment of cystic fibrosis patients.

Pseudomonas aeruginosa is the most common bacterium causing lung infections in people with cystic fibrosis. By the age of 17, nearly 70 percent of people with cystic fibrosis have *P. aeruginosa* in their lungs. Chronic infection leads to a vicious cycle. *P. aeruginosa* infections cause lung inflammation, which causes more mucus secretion. More mucus secretion and lung damage leads to further lung obstruction, which encourages the growth of more bacteria, causing additional deterioration of lung function. Although the rate of decline in lung function (FEV₁) varies from person to person, it is estimated to be between 1.4 and 4 percent per year. Adolescents may lose even more lung function over the course of a year.

In most people with cystic fibrosis, chronic lung infections cause gradual destruction of lung tissue. This leads to progressive lung disease, and eventually, respiratory failure. The Cystic Fibrosis Foundation estimates 95 percent of people living with cystic fibrosis die of respiratory failure. Cystic fibrosis patients also sometimes experience acute flare-ups, or exacerbations, of their pulmonary symptoms. These exacerbations often lead to a more rapid decline in lung function, and are the primary reason for hospitalization among people with cystic fibrosis. Finally, cystic fibrosis also affects other areas of the body, including the pancreas, sweat glands and reproductive organs.

Comments

1. Clinical investigations must be conducted to show the safety and effectiveness of the proposed drug product, which differs in strength, concentration, volume and formulation from TOBI.

The Suitability Petition should be denied because clinical investigations must be conducted to show the safety and effectiveness of the proposed drug product.¹ The proposed changes in drug concentration and volume to be administered, as well as a significantly modified formulation are not supported by the approved labeling for TOBI, nor is the use of a new, unapproved delivery system with a tobramycin solution for inhalation. Chiron recognizes the FDA Office of Generic Drugs' (OGD) long-standing position that solutions for oral inhalation must be qualitatively (Q1) and quantitatively (Q2) the same as the reference drug, where Q1 denotes the identical active and inactive ingredients as in the reference listed drug and Q2 denotes inactive ingredient concentrations within $\pm 5\%$ of those in the reference listed drug, in order to be eligible for review and approval under an ANDA.

¹ 21 C.F.R. §3.2(e)(1)(i).

Consistent with this position, and with current FDA policy and guidelines regarding nasal and inhalation drug products, especially those with complex pharmacokinetic (PK) and pharmacodynamic (PD) relationships, establishing the pharmaceutical equivalence of a tobramycin solution for inhalation with a different concentration, volume and formulation to TOBI, to be administered with a different inhaler, would require *in vivo* and other testing to assure the safety and efficacy of the new formulation. The administration of tobramycin by inhalation is a complex process involving interactions of the formulation, the device, and patient characteristics. *In vitro* testing would be insufficient to ensure that two different formulations will deliver identical amounts of the active ingredient to assure the equivalent or improved safety and efficacy of tobramycin after inhalation. Clinical studies with clinical endpoints would be required to establish the safety and efficacy of any tobramycin solution for inhalation for the management of CF patients with *P. aeruginosa* that differs from TOBI in formulation, concentration, volume, duration of administration, or change in dosing interval.

The FDA has concurred with this assessment historically. TOBI is approved at a concentration of 60mg/mL in a 5 mL volume, while the proposed drug product would be marketed in a 100 mg/mL concentration in a 1.9 ml volume. When Chiron undertook development of a more concentrated (120 mg/mL) formulation of tobramycin solution for inhalation, the inactive ingredients in the new formulation were identical to the TOBI[®] formulation and the device recommended for use was the same. The Center for Drug Evaluation and Research (CDER) Division of Anti-Infective Drug Products and Division of Pulmonary Drug Products nevertheless requested an evaluation of systemic effects (through a phase 1 PK study) and local effects (through a phase 2/phase 3 clinical efficacy and safety study) of the more concentrated tobramycin solution. The FDA's insistence upon completion of clinical trials with true clinical efficacy endpoints was a significant validation that long term clinical testing is the ultimate gold standard to demonstrate the efficacy and safety of a modified, higher strength formulation of tobramycin solution for inhalation in the absence of a clear PK/PD relationship.

2. The proposed changes in drug concentration, volume and formulation from TOBI, without conducting safety and efficacy trials, would jeopardize the safe and effective use of the product and would require significant labeling changes.

The Petition should be denied because it proposes dosing and administration of the proposed drug product in a manner that would inevitably lead to product substitution for TOBI and to the use of the proposed drug product with currently marketed nebulizers commonly used by patients with CF. TOBI, for example, is specifically formulated and approved for inhalation using only a PARI LC PLUS[™] Reusable Nebulizer and a DeVilbiss Pulmo-Aide[®] air compressor. As the Petition proposes use of a different and unapproved inhaler for a substantially shorter administration time with the proposed drug product than that of the reference listed drug, and proposes to limit use of the proposed drug product to this different and unapproved inhaler, the proposed drug product would create a new risk of inadvertent and rapid tobramycin overdosing by patients with CF. Absent significant and

prominent labeling changes to warn patients of this risk and absent demonstration through adequate and well controlled clinical studies that the proposed changes do not affect the safety or efficacy of the proposed drug product used in combination with the different, unapproved device, product substitution of the proposed drug product for TOBI could expose patients to significant risks of toxicity and adverse events, including but not limited to hearing loss.

Toxicities of significant concern associated with systemic exposure to tobramycin have been well described, and include eighth cranial nerve damage resulting in loss of hearing and/or vestibular disturbances, and kidney damage characterized by renal tubular degeneration. TOBI is associated through clinical data and experience with a risk of auditory dysfunction and ototoxicity. In postmarketing experience, some 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. Although there were no reports of kidney damage during the phase 3 trial for TOBI, post-marketing experience suggests that acute renal failure consistent with aminoglycoside toxicity can occur with TOBI administration, resulting in redistribution of drug from the site of application to the systemic circulation.

For these reasons, the proposed changes in strength, volume to be administered and formulation present substantial questions of product safety and toxicity that would require clinical studies to assure that the systemic exposure of the proposed drug product is less than or equal to that seen with the TOBI formulation. These findings would also require significant changes to the approved labeling of TOBI, including but not limited to a detailed warning statement, to minimize the substantial risks to CF patients from product substitution and the inappropriate use of the proposed drug product with currently marketed nebulizers. Conforming changes would also be essential to the TOBI Patient Medication Guide, which provides detailed instructions for the proper use and administration of TOBI with the approved LC PLUS nebulizer, the only nebulizer used in clinical evaluations of TOBI submitted to the FDA. The Petition should consequently be denied on the grounds that significant labeling changes would be required to address this newly introduced safety problem, which would arise from the changes in product strength and formulation proposed in the petition.²

3. Approval of the proposed new drug and device combination product would require submission of a New Drug Application.

The Petition should also be denied on the grounds that it seeks permission to file an ANDA for a new combination product.³ The petitioner specifically describes their intent to file an ANDA for both “a change in concentration of the formulation and a change in the

² 21 C.F.R. §3.2(e)(1)(iv).

³ 21 C.F.R. §3.2(e)(3).

inhaler” from TOBI, the reference listed drug.⁴ According to the Petition, the proposed drug product would be administered with the eFlow™ inhaler manufactured by PARI. Since the eFlow inhaler is not approved or cleared for marketing by the FDA as a delivery system for any drug product, much less a tobramycin solution for inhalation, the petitioner is inappropriately requesting permission to file an ANDA for an unapproved new drug and device combination product. Such a combination product would require filing of a New Drug Application (NDA) because it requires use of a novel delivery system and because of the need for clinical trials to change the labeling of the approved reference listed drug.⁵

According to the Petition, this unapproved new drug formulation and device combination product would purportedly deliver a respirable dose equivalent to the reference-listed drug in a shorter time of administration. The petition provides no substantiation for this specific claim. Devices used to deliver drugs for pulmonary administration can have a large impact on the size of the droplets or particles containing the drug, which in turn affects the deposition of the drug in the lung, systemic absorption and airway reactivity. The delivery of drug to the lung is also affected by such factors as the patient’s disease state and severity as well as lung function. By definition, use of the eFlow inhaler will change the rate of aerosol delivery, and the density of the aerosol that is administered, relative to the LC PLUS nebulizer approved for use with TOBI. More importantly, those parameters that define the aerosol particle size distribution of the LC PLUS when used with TOBI, such as mass median diameter (MMD) and geometric standard deviation (GSD), cannot be exactly reproduced with any new inhaler, including the eFlow.

These factors have been fully acknowledged in CDER’s recent guidance on locally acting nasal drugs.⁶ In conjunction with the performance of a specific nebulizer, small changes in formulation parameters such as osmolality, pH, and inactive ingredients are likely to produce changes in the delivery pattern and therefore have the potential to impact the safety and efficacy of inhaled drug products. Currently, there are no *in vitro* analytical tools to evaluate what level of change in formulation is sufficient to impact local and systemic deposition to produce significant changes in safety and efficacy. For these reasons, an ANDA for a tobramycin solution for inhalation that differs in any meaningful respect from the approved tobramycin solution for inhalation product would be substantively and materially incomplete without supporting clinical trial data to demonstrate safety and efficacy. Therefore, because the proposed drug product is intended to be administered only with a specific unapproved or uncleared nebulizer, the petition should be denied and an NDA should be required to provide the clinical evidence necessary to establish of the safety and

⁴ TOFIN™ ANDA Suitability Petition, Docket No. 2004P-0131, March 11, 2004, p. 1.

⁵ 21 C.F.R. §3.2(e)(3) defines combination products to include “[a] drug... packaged separately that according to its... proposed labeling is intended for use only with an approved individually specified... device... where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose”.

⁶ Center for Drug Evaluation and Research, Guidance for Nasal Administration of Locally Acting Nasal Drugs, April 2003.

efficacy of the proposed drug product for the treatment of CF patients with *P. aeruginosa* infection.

4. The Petition misappropriates findings of clinical studies conducted by Chiron and misstates their clinical relevance and significance.

The Petition inappropriately incorporates and relies upon clinical studies conducted by or for Chiron in a manner that misstates their clinical relevance to the proposed drug product. The petition references and includes descriptions of two different short-duration *in vivo* studies, one with TOBI and an experimental delivery device and another with a more concentrated formulation of tobramycin with the approved delivery device for TOBI, as evidence of safety and equivalency of respirable dose for the proposed drug product. The studies were undertaken as part of the previously cited development of a more concentrated (120 mg/mL) formulation of tobramycin solution for inhalation by Chiron (see *supra* 1.) and the descriptions of the studies included in the Petition are drawn from a patent application filed by Chiron Corporation.⁷

It must be emphasized that neither study is of direct relevance to the petition because neither study was conducted with the actual proposed drug product or with the uncleared or unapproved inhaler intended for use with the proposed drug product. For example, the study cited in appendix I of the Petition was a comparison of TOBI with a tobramycin solution for inhalation in a 120 mg/mL concentration in a 3.5 mL volume delivered by a PARI LC PLUS jet nebulizer and an Invacare Mobilaire™ compressor. In contrast, the petition has been filed on behalf of a proposed drug product with a 100 mg/mL concentration in a 1.9 ml volume delivered by the unapproved eFlow inhaler.

The second study cited in the petition was conducted using a decreased volume of TOBI and an experimental inhaler. The device used in this second study employed aerosol generation technology similar, *but not identical*, to that of the unapproved eFlow inhaler proposed for use in the Petition. The device used in the second study differed from the eFlow in several important aspects that would affect the delivered dose. In particular, aerosol generation by the device was actuated by inhalation, while the eFlow generates aerosol continuously throughout a treatment.

Neither of the referenced studies were conducted with the intention of demonstrating safety or efficacy comparable to TOBI and the PARI LC PLUS, the approved product and approved delivery system, but rather were intended as initial studies to rationalize a dose for subsequent complete clinical evaluations of safety and efficacy. The studies consequently provide no substantiation or assurance of the safety or effectiveness of the changes in product strength and total drug content, formulation, dosing regimen, and method of administration proposed in the petition.

⁷ WO 02/094217 A1 (November 28, 2002).

Finally, the two studies were not conducted by or for the petitioner, and the petitioner has not obtained a right of reference for use of the results from the studies. Even if the studies had been conducted with the proposed drug product or with the uncleared or unapproved inhaler intended for use with the proposed drug product, the petitioner would be unable to provide FDA with the data underlying its reports of the studies and the Agency would be unable to audit the investigations. For these reasons, the Petition relies inappropriately on the two clinical studies.

Conclusion

Chiron believes that the proposed changes in strength, volume to be administered and significantly modified formulation raise questions of safety and effectiveness and require that investigations be conducted to assure the proposed drug product is safe and effective. The proposed changes would also require significant labeling changes to address the new potential for tobramycin overdose and the heightened patient risk of toxicity and adverse events, including but not limited to hearing loss. Additionally, the proposed drug product and its administration with the unapproved delivery system is a combination product under the FDCA, requiring submission and approval of an NDA to permit its legal marketing. For these reasons, the petition should be denied under section 505(j)(2)(C) of the FDCA.

We appreciate your review of these important issues and would be happy to provide any additional information that you may request.

Sincerely,



Michael C. Scaife, Ph.D., Vice President
Chiron Corporation - BioPharma Regulatory Affairs