

DIVISION DIRECTOR MEMORANDUM

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To: Members, Pulmonary-Allergy Drugs Advisory Committee

Subject: Overview of the FDA background materials for NDA #21-395, application for tiotropium bromide inhalation powder for the treatment of chronic obstructive pulmonary disease

Thank you for your participation in the upcoming Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting to be held on September 6, 2002. As members of the PADAC you provide important expert scientific advice and recommendation to the US Food and Drug Administration (the Agency) related to the approval of a drug product. The upcoming meeting is to discuss the NDA from Boehringer Ingelheim Pharmaceuticals, Inc., seeking an approval for tiotropium bromide (Spiriva) inhalation powder for the treatment of bronchospasm and dyspnea associated with chronic obstructive pulmonary disease (COPD). The proposed indication of dyspnea is unique for a COPD drug.

The material to be discussed in this meeting and the opinions we are seeking from you are solely related to clinical issues of tiotropium. Please bear in mind that in the regulatory decision making process to determine approvability of a drug product, the Agency takes into consideration various factors in addition to clinical issues, such as Chemistry, Manufacturing and Controls of a drug product, preclinical considerations, etc. Those are not being discussed in this meeting. Your opinion expressed in this meeting will be a very important part of the decision making process to determine approvability of tiotropium.

Attached are the background materials for the meeting. The background materials included are the clinical briefing document, clinical pharmacology and biopharmaceutics briefing document, a review article on COPD, an article on measurement of dyspnea, and the product labels of several drugs currently approved in the United States for the treatment of COPD. The drugs currently approved in the United States for the treatment of COPD are short acting beta2-adrenergic agonists albuterol, bitolterol, metaproterolol, pirbuterol, and terbutaline; long-acting beta2-adrenergic agonists salmeterol and formoterol; short-acting anti-cholinergic agent ipratropium; and theophylline.

This memorandum summarizes the contents of the background material, and the key issues and question for discussion at the meeting. The materials prepared by the Agency contain findings and opinions based on reviews of submission by the Applicant. These represent preliminary findings, and do not represent final position of the Agency. Indeed, an important

piece of our thinking on the application is the opinions and the input that we receive from you in this meeting.

Tiotropium is a long-acting anticholinergic agent. Spiriva is a dry powder formulation of tiotropium bromide, which is intended for administration by oral inhalation route using a reusable, hand-held, breath actuated device called the HandiHaler. The proposed dose is one 18-mcg capsule once daily. No formulation of tiotropium has been approved for use in humans in the United States. The Applicant studied the safety and efficacy of tiotropium in six phase 3 trials. Two trials were conducted in US, were one-year in duration, and were placebo-controlled. Two trials were conducted in Europe, were one-year in duration, and were active (ipratropium bromide MDI)-controlled. Two trials were multinational, were six months in duration, and were placebo- and active (salmeterol xinafoate MDI)-controlled. A total of 4,124 subjects participated in the clinical program of tiotropium, of which 3,411 were COPD patients, of which 1,723 were exposed to tiotropium. Safety findings are described in the clinical briefing document. Adverse events related to anticholinergic effects such as dry mouth, urinary effects, and constipation were more common in the tiotropium treated patients. In the pivotal clinical trials there were subtle suggestions that tiotropium may be associated with adverse cardiac effects. Holter monitoring was done in only one supporting study. We ask you to give your opinion on the adequacy of the safety database, specifically the cardiac safety database, of tiotropium.

The phase 3 trials for tiotropium have attempted to support both the efficacy of the drug as a bronchodilator, and the efficacy of the drug in the treatment of dyspnea associated with COPD. Each of the six trials have addressed the bronchodilator activity by assessing FEV1 measure as a primary or as a co-primary variable, and by secondary variables such as forced vital capacity, peak expiratory flow rates, and rescue albuterol use. The primary or co-primary variable was the change from baseline in the trough (pre-dose) FEV1 value. An advantage in using the trough FEV1 value is that it can provide support of the proposed dosing interval by demonstrating continued efficacy at the end of the dosing interval. Disadvantages in using the trough FEV1 value is that there is no consensus regarding the minimum magnitude of effect that can constitute a clinically meaningful effect, and efficacy is not determined during peak response where there is a general consensus that at least a 12% and 200 mL increase in FEV1 constitute a clinically meaningful bronchodilating effect. However, in some of the clinic visits serial spirometry were done, which allows for assessment of the peak response and durability of the response. We ask you to give your opinion whether the data provide convincing evidence that tiotropium provides a clinically meaningful bronchodilator effect when used in the treatment of COPD.

The proposed dyspnea indication is based on assessment of the Mahler Transitional Dyspnea Index (TDI). In four of the six phase 3 trials (the four one-year trials), TDI was assessed as a secondary efficacy variable, where the TDI data was analyzed using mean values. After noticing encouraging results in the TDI in the four phase 3 trials, the Applicant decided to add TDI as a co-primary efficacy variable in the remaining two trials (the 6-month multinational placebo- and salmeterol-controlled trials). The protocols of these two trials were amended to include TDI as a co-primary variable after the trials were completed but before the blind was broken. The variable was assessed as focal TDI score at the end of the

6-month trial. The focal TDI score is the sum of the individual scores of the three components of the TDI – functional impairment component, magnitude of task component, and magnitude of effort component. In these two trials, the TDI analyses were based on responder analyses, where a threshold of 1 in the TDI was the definition of a responder. The applicant's claim of the dyspnea indication is based primarily on these two 6-month trials. In evaluating the Applicant's claim of a dyspnea indication for tiotropium we ask you to consider the aspects of development, validation, and statistical analysis of the TDI instrument used in the trials. We ask you to give a general opinion on what types of data would constitute substantial and convincing evidence of a clinically meaningful benefit with regard to dyspnea in patients with COPD. We also ask you to give a specific opinion whether the data provide convincing evidence that tiotropium provides a clinically meaningful effect on the symptom of dyspnea when used in the treatment of COPD.

The purpose of this PADAC meeting is to discuss the adequacy of the safety and efficacy data submitted by Boehringer Ingelheim to the Agency to support the approval of tiotropium for COPD in the United States. While all clinical issues related to tiotropium are open for discussion, we are asking for a detailed deliberation on the dyspnea claim, because the specific indication of dyspnea is unique amongst all drugs that are currently approved in the United States for COPD. The drugs currently approved for COPD generally refer to the treatment of bronchospasm associated with COPD, intentionally focusing on the bronchodilator activity of the drugs, and avoiding the use of language that would imply that the drugs have been shown to treat a specific symptom of the disease, or the disease itself.

At the PADAC meeting, the applicant will present an overview of the clinical data in support of the proposed claims, followed by the Agency's presentation of the clinical data. Since a larger part of the discussion is expected to cover the claimed dyspnea indication, the FDA will have a specific presentation on the Mahler TDI instrument, followed by presentation of the overall clinical program. The presentation of the overall clinical program will highlight some salient pharmacokinetic and pharmacodynamic features of tiotropium, and an overview of the phase 3 clinical trials covering the extent and findings of the safety database, the efficacy findings in regard to bronchodilator effect, and efficacy findings in regard to dyspnea effect. I request you to keep in mind the following questions that will be discussed and deliberated upon following the presentation and discussion.

1. Is the safety database for tiotropium bromide inhalation powder for the treatment of COPD patients adequate?
 - a) If the safety database is not adequate, what further safety data should be obtained?
 - b) Which of the safety data should be obtained prior to approval?
2. Are there specific safety concerns regarding the use of tiotropium bromide inhalation powder in the COPD patient population that merit specific attention in the product label.
3. Do the data provide substantial and convincing evidence that tiotropium bromide inhalation powder provides a clinically meaningful bronchodilator effect when used in the chronic treatment of patients with COPD?

4. Do the data provide substantial and convincing evidence that tiotropium bromide inhalation powder provides a clinically meaningful effect on the symptom of dyspnea in patients with COPD?
5. In general, what type and amount of data would constitute substantial and convincing evidence of a clinically meaningful benefit with regard to the symptoms of dyspnea in patients with COPD?

Please note that the questions above are preliminary and may change prior to the meeting. Final questions will be posted before the meeting. Some questions, such as the main stem of question 1, and questions 3 and 4, should generate a binary yes or no answer, and will be voted on by the voting members of the Committee.

We look forward to a very interesting meeting and again thank you for your time and commitment in this important public health service.