Pulmonary Allergy Drugs Advisory Committee
September 6, 2002
Holiday Inn Gaithersburg
Minutes

New Drug Application (NDA) 21-395, Spiriva (Tiotropium bromide) by Boehringer-Ingelheim for chronic obstructive pulmonary disease (COPD).

COMMITTEE
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INDUSTRY REPRESENTATIVE
William Kennedy, Ph.D.

EXECUTIVE SECRETARY
Kimberly Littleton Topper

CONSULTANTS (voting)
James K. Stoller, M.S., M.D.
Donald Patrick, Ph.D.

GUEST SPEAKER (non-voting)
Michael Schatz, M.D.

FDA PARTICIPANTS
Robert Meyer, M.D.
Badrul Chowdhury, M.D.
Eugene Sullivan, M.D.
Lisa Kammerman, Ph.D.

I certify that I attended the September 6, 2002 meeting of the Pulmonary-Allergy Drugs Advisory Committee and that these minutes accurately reflect what transpired.

/S/
Kimberly L. Topper, MS
Executive Secretary

Date

/S/
Mark S. Dykewicz, M.D.
Chairman

Date

A verbatim transcript of this meeting is available for more detailed information.

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New Drug Application (NDA) 21-395, Spiriva (Tiotropium bromide) by Boehringer-Ingelheim for chronic obstructive pulmonary disease (COPD).

The meeting was called to order by Dr. Mark Dykewicz at 7:30 AM. Introductions of the committee members, consultants and guests were made and the Conflict of Interest statement was read into the record. Dr. Robert Meyer welcomed the committee and thanked them for attending and Dr. Badrul Chowdhury set the stage for the topic of the day's discussions.

Boehringer Ingelheim had the following presentations:

Introduction and Overview — Dr. Burkhard Blank

Dr. Blank provided the BI introduction to the topic by explaining what COPD is and giving statistics about the disease progression and mortality rates. He stated their major topics for the day were 24-hour bronchodilation, the relief of dyspnea and the safety profile. The proposed indication was presented as:

SPIRIVA® (tiotropium) is indicated for the long-term, once-daily, maintenance treatment of bronchospasm and dyspnea associated with Chronic Obstructive Pulmonary Disease (COPD) including bronchitis and emphysema.

He then introduced each speaker and the topics they would present.

Bronchodilator Efficacy in COPD — Dr. Bernd Disse

Dr. Disse concluded Tiotropium once-daily provides sustained improvement of spirometric measures for 24 hours, patient improvements were maintained over one year, with no evidence of tachyphylaxis, and secondary endpoints and exploratory analyses show improvements of related lung function, exacerbations, and the patient health status.

Quantification of Dyspnea — Dr. Paul Jones

Dr. Jones discussed the quantification of dyspnea and covered the measurement of breathlessness, the validation of BDI and TDI and the identification of clinically significant thresholds.

Dyspnea and Related Measures — Dr. Theodore Witek

Dr. Witek discussed the use of dyspnea assessments in clinical trials stating the long-term assessments are particularly important in chronic disease maintenance treatment. He also stated that the instrument needs to be practical in a multi-center and multi-national setting, dyspnea assessment needs to be in context of a clinic visit and supportive assessments should be included to assist in determining validity and consistency. He closed by stating that the effect of tiotropium on dyspnea was supported by the use of a validated instrument, prespecification of a primary endpoint, statistical significance observed in two independent studies, meaningful change supported by mean responses and dyspnea response reflected in related measures.

Clinical Safety Evaluation Dr. Steven Kesten

Dr. Kesten discussed the clinical safety evaluating stating that tiotropium has had extensive clinical safety evaluations with a large patient population and long-term exposures. He indicated that the safety profile is similar to that of ipratropium. The safety data included long-term studies of 1,308 tiotropium treated patients, adverse events were consistent with anticholinergic pharmacology, there were no associations of treatment with life-threatening events and the tiotropium safety profile is consistent with established inhaled anticholinergic therapy.

Clinical Perspective Dr. James Donohue

Dr. Donohue discussed the typical patient with COPD and the disease progression and the challenges in demonstrating dyspnea relief in clinical studies. He stated that he believes that tiotropium would be a valuable addition to the medical armamentarium.

Conclusions Dr. Burkhard Blank

Dr. Blank them concluded the BI presentations by stating the major topics for discussion were the safety profile, the 24-hour bronchodilation and the relief of dyspnea.

The Food and Drug Administration had the following presentations:

Transition Dyspnea Index (TDI) Dr. Lisa Kammerman

Dr. Kammerman discussed the Baseline Dyspnea Index (BDI)/Transition Dyspnea Index (TDI), the history of the use of the TDI as a co-primary endpoint in the tiotropium program, and FDA concerns regarding the BDI/TDI, including clinical trial design issues, development and validation issues, implementation issues, and the importance of establishing a threshold for a clinically meaningful difference. She concluded that the patient level issues were the unknown level of patient involvement in the development of the instrument and in the determination of a minimal clinically important difference. The interviewer level issues were the blinding of patient status, training of interviewers, open-ended questions, non-standardized questions, recall to baseline and the review of the SGRQ before completion of the TDI. She stated that the clinically meaningful difference appeared to be determined with no prespecified plan and no patient involvement to determine the clinically meaningful difference. There were also concerns about who administered the TDI and the impact of multinational populations as it impacts development, validation and interpretation of results.

PK/PD, Safety & Efficacy Dr. Eugene Sullivan

Dr. Sullivan covered the proposed indications, the PK/PD characteristics, a brief overview of the P3 clinical program, and the safety and efficacy findings. He summarized his findings by stating some of the PK/PD features of tiotropium are unique among inhaled bronchodilators. Concerns about safety are, the dry mouth, which shows interactions with age and gender and is more frequent in tiotropium than with ipratropium, a higher frequency of AE's with tiotropium than with placebo and the possible effect on the heart rate/rhythm may merit further evaluation.

Dr. Sullivan's discussions on the efficacy showed that Spiriva® appears to provide clinically meaningful bronchodilation, the duration of action supports once-daily dosing, the maximum bronchodilator effect is reached after multiple daily doses and it has an demonstrable statistical effect on the TDI however, the clinical significance of this effect is not known.

Following the presentations the committee questioned the presenters for clarification on specific points of the presentations.

The Open Public Hearing had one presenter, Vlady Rozenbaum, Ph.D. He encouraged getting Spiriva® to the market as soon as safely possible. There were also 55 e-mails and letters that were given to the committee from others that would like to see Spiriva® on the market in the US.

The committee started the discussion of the issues and both FDA and BI participated in the discussions. The Committee members then moved on to the questions.

1. Is the safety database for tiotropium bromide inhalation powder for the treatment of COPD patients adequate?

YES ___8_____ NO ____3_____

Schell - yes	**Chinchilli – yes**	**Apter – yes**	**Swenson – no**
Dykewicz – yes	**Stoller – yes**	**Joad – no**	**Morris – no**
Atkinson – yes	**Parsons – yes**	**Patrick - yes**	

   A) If not, what further safety data should be obtained?
      - **Regarding the renal excretion of the drug , there is a concern in patients with renal insufficiency**
      - **Phase 4 studies are needed to track urinary retention or urinary difficulty, fecal impaction, tachycardia and atrial fibrillation**
      - **Phase 4 studies in non-tested populations and labeling to indicate the drug is not approved in those populations**
      - **Diabetes and hyperglycemia should be monitored in the appropriate patients**

   B) Which of the safety data should be obtained prior to approval?
      - **Would like to see safety data on excluded subsets (cardio, kidney)**
      - **There is a data gap due to the lack of Holter monitors – it would better if there were more Holter data**
      - **Would like to see the numbers of COPD patients in the excluded groups (concern the drug will be used in then when approved and no data is available**)

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?

- **Serious concerns about widespread use in patients such as cardiac patients without additional data**
- **Phase 4 studies should be required for patient populations excluded from original study**
- **Education of health practitioners on safety data and populations of concern**
- **Education to prescribers that it is not like any of the other drugs that are currently out there**

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?

Yes ___11_____ No ___0_____

Schell – yes	**Chinchilli – yes**	**Apter – yes**	**Swenson – yes**
Dykewicz – yes	**Stoller – yes**	**Joad – yes**	**Morris – yes**
Atkinson – yes	**Parsons – yes**	**Patrick – yes**	

- **Using the trough FEV response as a primary endpoint is a useful endpoint**

4. Do the data provide substantial and convincing evidence that tiotropium bromide inhalation powder provides a clinically meaningful effect for the symptom of dyspnea in patients with COPD?

Yes ___0_____ No ____11____

Schell – no	**Chinchilli - no**	**Apter- no**	**Swenson- no**
Dykewicz- no	**Stoller – no**	**Joad – no**	**Morris - no**
Atkinson – no	**Parsons – no**	**Patrick - no**	

5. In general, what quality and quantity of data would constitute substantial and convincing evidence of a clinically meaningful benefit for the symptom of dyspnea in patients with COPD?

Quality:

- **Validated in a diverse population**
- **Define dyspnea very specifically and clearly**
- **Must have substantial data on minimally important differences**
- **Use combination clinical interview and patient report**
- **Tie concept to something reproducible, objective and that applies to the dyspnea scale**
- **Address each of Dr. Kammerman's concerns and must be reproducible in different populations**
- **Define the longitudinal properties of the BDI**

- **Instrument that is patient reported symptoms and asks if specific changes are significant to the patient**
- **Patient evaluations are critical and they should be questioned about how much value the regimen had to them and what the value was and what would they be willing to sacrifice**

Quantity

- **The quantity of data presented by BI were good but they must be rigorous in the data collected and the way it is captured for analysis**

The Chair and FDA staff thanked everyone for their participation and the meeting was adjourned at 3:05 PM.