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Integrated Review of Efficacy

randomized to receive tiotropium or placebo once daily in the morning. Eligible patients had a history of COPD, a smoking history of ≥ 10 pack-years, age ≥ 40 years, and $FEV_1 \leq 65\%$ of predicted and $\leq 70\%$ of FVC. Baseline bronchodilator reversibility was not assessed. Spirometry was performed at baseline, and after 1, 7, 13, 37, and 49 weeks of treatment. On these test days spirometry was performed at one-hour prior to dosing, immediately prior to dosing, and at 30, 60, 120, and 180 minutes after dosing. The pre-specified primary efficacy endpoint was the "trough FEV_1 response" at the end of the first 13 weeks of treatment. The "trough FEV_1 response" was defined as the change from baseline in the mean of the two FEV_1 values at the end of the dosing interval (approximately 23 and 24 hours post-dosing). Secondary efficacy endpoints included the trough FEV_1 response at other timepoints, the average and peak FEV_1 response for the first 3-hours post-treatment on each test day, individual FEV_1 and FVC values, weekly mean PEFr measured by the patient at home twice daily, physician's global evaluation, COPD symptom scores (wheezing, shortness of breath, coughing, and tightness of chest), rescue albuterol use, number of nocturnal awakenings during the first 13 weeks, number and length of COPD exacerbations and hospitalizations for respiratory disease, the Saint George's Respiratory Questionnaire (SGRQ), and pharmacoeconomic variables.

Most of the patients in these studies were White (91.9% and 96.7%), and the majority were men (66.7% and 66.4%). At screening, these patients had a mean FEV_1 of approximately 1 liter, and a ratio of FEV_1/FVC of approximately 45%.

Primary Endpoint: Trough FEV_1 Response (liters), Week 13 (Studies 205.114/205.117 and 205.115/205.128)			
Study	Tiotropium	Placebo	p-value
205.114/205.117	0.11	-0.03	0.0001
205.115/205.128	0.13	-0.01	0.0001

Both of these studies demonstrated that tiotropium was superior to placebo on the pre-specified primary endpoint, trough FEV_1 response after 13 weeks of treatment ($p=0.0001$). The mean trough FEV_1 response in the tiotropium group was 0.11 liters (compared with -0.03 liters in the placebo group) in Study 205.114/205.117, and 0.13 liters (compared with -0.01 liters in the placebo group) in Study 205.115/205.128. These data indicate that tiotropium has a statistically significant bronchodilator effect at the end of the proposed dosing interval. It should be noted that the Division has not previously taken a position regarding the magnitude of effect that would be considered to be clinically meaningful for the end-of-dosing interval FEV_1 . In assessing acute bronchodilator efficacy, a threshold of at least 12% and at least 200ml is commonly used to determine a clinically meaningful bronchodilator effect. However, it would not seem reasonable to use this threshold for the end of the dosing interval. *Thus, the analysis of the primary endpoint established that the bronchodilator effect of tiotropium remains statistically significant at the end of the dosing interval. The magnitude of that effect is small compared to what would be expected if this measure were taken at peak effect, but is probably clinically meaningful at the end of the dosing interval.*

Secondary spirometry endpoints included trough FEV_1 response after 1, 7, 25, 37, and 49 weeks of treatment. At each of these timepoints, tiotropium was statistically superior to placebo ($p=0.0001$), with effect sizes (tiotropium minus placebo) of 0.11 to 0.16 liters. These data

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further support the conclusions regarding end-of-dosing interval efficacy that were drawn from the primary efficacy endpoint analysis.

Insight into the early post-dose bronchodilator effect of tiotropium can be drawn from the 3-hour serial spirometry performed on each test day. In both studies, tiotropium was superior to placebo in regard to the mean average FEV₁ response during the 3-hour serial spirometry, on all test days (p=0.0001). Because this parameter is an average of several spirometry measures, interpretation of the effect size is less intuitive.

Perhaps more helpful is the information derived from the analyses of the peak FEV₁ data. In both studies, tiotropium was superior to placebo in regard to the mean peak FEV₁ response on all test days (p=0.0001). However, the mean treatment effect size (i.e. tiotropium effect minus placebo effect) was small, ranging from 0.15 liters on test day 1, to 0.19-0.22 liters on subsequent test days. It should be noted that in assessing for what is considered a clinically meaningful degree of bronchodilation (using the threshold of 12% and at least 200ml), it is not customary to consider placebo responses. Thus, the absolute increase in FEV₁, without subtraction of placebo effect, is customarily used. In these studies, the mean peak FEV₁ response was 0.24 liters on test day 1, and ranged from 0.25 to 0.31 liters on subsequent test days. This would support the assertion that, despite the relatively small difference between tiotropium and placebo, tiotropium is associated with a clinically meaningful degree of bronchodilation on all test days.

One further insight into the pharmacodynamics of tiotropium can be obtained from the peak FEV₁ data. While the mean peak FEV₁ on test day 1 was 0.24 liters in the tiotropium groups, the mean peak FEV₁ at each of the four individual test day 1, post-dose assessments was <0.20 liters. This unusual circumstance is due to the fact that patients reached their personal peak FEV₁ values at differing time points (see table below).

Percentage of Patients Who Reached Their Peak FEV ₁ at Each Timepoint (Test Day 1) [Submission dated 7/16/02; page 8]				
Timepoint	Tiotropium		Placebo	
	205.114/205.117	205.115/205.128	205.114/205.117	205.115/205.128
30 minutes	14.7%	18.8%	26.2%	30.0%
1 hour	20.4%	19.2%	25.1%	25.0%
2 hours	29.7%	29.2%	26.7%	19.4%
3 hours	35.1%	32.8%	22.0%	25.6%

Other measures of pulmonary function also supported the bronchodilator efficacy of tiotropium. In both studies, tiotropium was also statistically significantly superior to placebo for the trough, average, and peak FVC responses on all test days. The FVC data from both studies suggested that the bronchodilator efficacy increased between Day 1 and Day 8. Daily morning and evening peak flow measurements were performed and recorded by the patients. For the morning peak flow measurements, tiotropium was statistically superior to placebo during approximately one-half of the weeks in one study (205.114/205.117), and during nearly all of the weeks in the other, with effect sizes ranging from 8 to 31 liters/minute. Tiotropium was statistically superior to placebo in regard to evening peak flow measurements, with effect sizes ranging from 13 to 40 liters/minute.

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Other evidence in support of the efficacy of tiotropium as a bronchodilator includes the reported use of as-needed supplemental albuterol. During each week of treatment, patients in the tiotropium group used statistically significantly fewer doses of as-needed albuterol. On average, patients in the tiotropium group used approximately 5-6 fewer doses of albuterol, compared with patients in the placebo group. Although in one study (205.114/205.117) patients in the tiotropium group reported statistically fewer nocturnal awakenings due to COPD symptoms during 7 of the 13 weeks this was assessed, in the second study, no effect on this variable was seen.

Despite the efficacy of tiotropium as a bronchodilator, in both studies there was no difference between tiotropium and placebo in regard to the number of patients with COPD exacerbations, time to COPD exacerbation, number of COPD exacerbation days, number of patients with hospitalization due to COPD, or number of hospitalizations due to COPD.

The studies also included two health-related quality of life assessments, the "disease-specific" St. George's Hospital Respiratory Questionnaire (SGRQ) and the non-disease specific Medical Outcomes Study SF-36. Differences between groups rarely reached the generally accepted threshold for a minimal clinically meaningful effect on the SGRQ, which was administered at baseline, and after 7, 13, 25, 37, and 49 weeks of treatment. The study reports did not describe analyses of the total SF-36 scores. Results for the "physical health" domains within the SF-36 were not consistent between studies.

Finally, in both studies the scores on the Physician's Global Evaluation were statistically superior in the tiotropium group on all test days. However, the clinical significance of the treatment effect seen (0.25 to 0.59 on a scale of 1-8) is not known.

ONE-YEAR, ACTIVE-CONTROLLED STUDIES (205.122A/205.126A and 205.122B/205.126B)

Two, identical, large, randomized, double-blind, active-controlled, parallel group studies examined the safety and efficacy of tiotropium (QD) versus ipratropium bromide (QID) administered for approximately 1 year (52 weeks) (Study 205.122A/205.126A and Study 205.122B/205.126B). Detailed reviews of these studies are located in the Appendix to this Medical Officer Review. In these studies, a total of 535 patients with COPD were, following a 2-week baseline period, randomized to receive either tiotropium inhalation capsules QD or ipratropium bromide MDI QID (2:1 randomization). Eligible patients had a history of COPD, a smoking history of ≥ 10 pack-years, age ≥ 40 years, and $FEV_1 \leq 65\%$ of predicted and $\leq 70\%$ of FVC. Baseline bronchodilator reversibility was not assessed. Spirometry was performed at baseline, and after 1, 7, 13, 26, 39, and 52 weeks of treatment. On test days during the first 13 weeks, spirometry was performed at one-hour prior to dosing, immediately prior to dosing, and at 30, 60, 120, 180, 240, 300, and 360 minutes after dosing. On the remaining test days, the serial spirometry ended after the 180-minute measure. The pre-specified primary efficacy variable was the "trough FEV_1 response," defined as the change from baseline in the mean of the two FEV_1 values at the end of the dosing interval (approximately 23 and 24 hours post-dosing). The protocol did not state which specific treatment visit would serve as the primary efficacy

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endpoint. Secondary efficacy endpoints included the average and peak FEV₁ response for the first 6-hours post-treatment at Weeks 1, 7, and 13, and the first 3-hours post treatment on the remaining test days, individual FEV₁ and FVC values, weekly mean PEFr measured by the patient at home twice daily, an Energy-Fatigue Questionnaire, rescue albuterol use, the Saint George's Respiratory Questionnaire (SGRQ), and pharmacoeconomic variables.

The great majority of patients were men (81.7% and 87.3%, in each study), and all patients except one were white. The baseline mean FEV₁ for all patients was approximately 1.2 liters, with an FEV₁/FVC ratio of approximately 45%.

Before discussing the efficacy results of these studies, two issues should be noted. First, in these studies the primary efficacy variable (trough FEV₁) was determined at a timepoint at which the active comparator, based on its known pharmacodynamic properties, would not be expected to be effective. The active comparator, ipratropium bromide, is indicated for use four times daily. Given the relatively long interval between the evening dose and subsequent morning dose of ipratropium, little if any bronchodilator effect is likely to be detected on morning pre-dose spirometry. The second issue is that, for US regulatory purposes, a new drug does not need to demonstrate superiority over existing drugs. Therefore, although the primary endpoint may be intrinsically biased to favor a longer-acting drug over a shorter-acting drug, in this circumstance, for regulatory decision-making, the ipratropium treatment group may be considered analogous to placebo. Presuming that treatment with ipratropium has no detrimental effect in terms of COPD efficacy endpoints, demonstrated superiority over ipratropium may be construed as superiority over placebo.

In both studies, tiotropium was statistically superior to ipratropium for the trough FEV₁ response at all test days. The difference in trough FEV₁ response between groups ranged from 0.11 liters to 0.18 liters.

Because these studies did not include a placebo treatment group, the post-dosing serial spirometry offer little data relevant to regulatory decision-making. This data will not be discussed further here, but is discussed for each study in the Appendix to this Review. Home morning and evening PEFr values were statistically superior in the tiotropium group during all of the weeks of one study (205.122B/205.126B), and during most of the weeks in the other. The effect sizes for these measures were variable.

The use of as-needed albuterol was not different between groups in one study (205.122B/205.126B), and was statistically lower in the tiotropium group for 36 of the 52 weeks of the other study. The effect on COPD exacerbations was not consistent. In one study (205.122A/205.126A), no difference between groups was observed in regard to the number of patients with COPD exacerbation, time to first COPD exacerbation, number of COPD exacerbations, number of COPD exacerbation days, number of patients with hospitalizations due to COPD, or number of hospitalization days for COPD. However, in the second study, the tiotropium group had significantly fewer subjects with COPD exacerbations, fewer COPD exacerbations, and fewer COPD exacerbation days. Also in that study, the time to first COPD

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exacerbation was longer in the tiotropium group. Hospitalizations due to COPD were not different.

The studies also included two health-related quality of life assessments, the “disease-specific” St. George’s Hospital Respiratory Questionnaire (SGRQ) and the non-disease specific Medical Outcomes Study SF-36. Differences between groups rarely reached the generally accepted threshold for a minimal clinically meaningful effect on the SGRQ, which was administered at baseline, and after 7, 13, 25, 37, and 49 weeks of treatment. The SF-36 did not demonstrate statistical differences between groups. Finally, the studies included a three-question “Energy Fatigue Questionnaire,” administered on test days 8, 50, 92, 182, 273, and 364. There were no statistically significant differences between groups on this questionnaire.

SIX-MONTH PLACEBO- AND ACTIVE-CONTROLLED STUDIES (205.130 and 205.137)

Two, nearly identical, large, randomized, double-blind, placebo- and active (salmeterol inhalation aerosol) controlled, parallel group studies examined the safety and efficacy of tiotropium versus placebo administered for six months (Study 205.130 and Study 205.137). These two studies differed only in that the former included post-dosing serial spirometry for 12 hours after dosing, whereas the latter included 3-hour post-dosing serial spirometry. Detailed reviews of these studies are located in the Appendix to this Medical Officer Review. In these studies, a total of 1207 patients with COPD were, following a 2-week baseline period, randomized to receive either tiotropium (18mcg QD), salmeterol xinafoate inhalation aerosol (50mcg BID), or placebo. Eligible patients had a history of COPD, a smoking history of >10 pack-years, age ≥ 40 years, and $FEV_1 \leq 60\%$ of predicted and $\leq 70\%$ of FVC. Baseline bronchodilator reversibility was not assessed. Spirometry was performed at baseline, and after 2, 8, 16, and 24 weeks of treatment. On these test days spirometry was performed at one-hour prior to dosing, 10 minutes prior to dosing, and at 30 minutes, 1, 2, 3, 4, 6, 8, 10, and 12 hours after dosing in Study 205.130. In Study 205.137, post-dose serial spirometry included only 3 hours after dosing. The pre-specified primary efficacy endpoints were the “trough FEV_1 response” and the focal score of the Mahler Transition Dyspnea Index (TDI), at the end of the 24 weeks of treatment. The “trough FEV_1 response” was defined as the change from baseline in the mean of the two FEV_1 values at the end of the dosing interval (approximately 23 and 24 hours post-dosing). Secondary efficacy endpoints included the TDI focal score on other test days, the trough FEV_1 response on other test days, the average and peak FEV_1 response on each test day, individual FEV_1 and FVC values, weekly mean PEFr measured by the patient at home twice daily, physician’s global evaluation, COPD symptom scores (wheezing, shortness of breath, coughing, and tightness of chest), rescue albuterol use, the shuttle walking test with Borg dyspnea rating scale, number and length of COPD exacerbations and hospitalizations for respiratory disease, the number of patients with at least one COPD exacerbation, the number of patients with at least one hospitalization for respiratory disease, the Saint George’s Respiratory Questionnaire (SGRQ), patient preference, and pharmacoeconomic variables.

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The majority of patients were men (74.6% and 77.9% in Study 205.130 and 205.137, respectively), and nearly all patients were white (99.5%). The mean age of the patients was approximately 64 years, and the mean screening FEV₁ was approximately 1.1 liters.

Before discussing the efficacy results of these studies, one important issue should be noted. Although these studies included three treatment arms, the pre-specified primary comparison was that of tiotropium versus placebo. This is appropriate because, from the regulatory perspective, it is this comparison that is most important. Therefore, this Integrated Review of Efficacy will focus on the comparison of tiotropium versus placebo. However, the study report also discusses the comparison of tiotropium versus salmeterol. In considering the findings of the tiotropium versus salmeterol comparison, one must keep in mind that one of the co-primary efficacy variables (trough FEV₁) was determined at a timepoint at which the active comparator, based on its known pharmacodynamic properties, would not be expected to be effective. The active comparator, salmeterol, is indicated for use twice daily. Given the relatively long interval between the evening dose and subsequent morning dose of salmeterol, little if any bronchodilator effect is likely to be detected on morning pre-dose spirometry.

In both studies, tiotropium was statistically superior to placebo for the trough FEV₁ response after 24 weeks of treatment. The mean trough FEV₁ response in the tiotropium group was 0.14 liters in Study 205.130, and 0.11 liters in Study 205.137. These data indicate that tiotropium has a statistically significant bronchodilator effect at the end of the proposed dosing interval. It should be noted that the Division has not previously taken a position regarding the magnitude of effect that would be considered to be clinically meaningful for the end-of-dosing interval FEV₁. In assessing acute bronchodilator efficacy, a threshold of at least 12% and at least 200ml is commonly used to determine a clinically meaningful bronchodilator effect. However, it would not seem reasonable to use this threshold for the end of the dosing interval. *Thus, the analysis of this co-primary endpoint established that the bronchodilator effect of tiotropium remains statistically significant at the end of the dosing interval. The magnitude of that effect is small compared to what would be expected if this measure were taken at peak effect, but is probably clinically meaningful at the end of the dosing interval.*

Tiotropium was also statistically superior to placebo on each of the serial spirometry measurements on all test days in both studies. Consistent with this, tiotropium was statistically superior to placebo in regard to the mean trough, average, and peak FEV₁ response on all test days in both studies. On the first test day, the mean peak FEV₁ response was 0.31 liters (Study 205.130) and 0.27 liters (Study 205.137). The difference between the tiotropium mean peak FEV₁ response and the placebo mean peak FEV₁ response was 0.19 and 0.16 liters on test day 1 in these two studies. The serial spirometry FVC data was consistent with the FEV₁ data. The patient-recorded daily PEFr data also supported the efficacy of tiotropium as a bronchodilator. In both studies, the mean weekly morning and mean weekly evening PEFr values were statistically superior in the tiotropium group, as compared to the placebo group. The differences between tiotropium and placebo ranged from 14.9 to 27 liters/minute for the morning PEFr, and from 21 to 33 liters/minute for the evening PEFr.

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Interestingly, in only one of the two studies was tiotropium statistically superior to placebo in regard to the number of puffs of as-needed albuterol used by the patients (Study 205.130).

In Study 205.130, there were statistically fewer COPD exacerbations and COPD exacerbation days in the tiotropium group as compared to placebo, but there was no statistically significant difference between these two groups in regard to the number of subjects with at least one COPD exacerbation. In Study 205.137 there were no significant differences between tiotropium and placebo in regard to the various expressions of COPD exacerbations. There were no notable differences between tiotropium and placebo in regard to hospitalizations for COPD in either study.

Tiotropium was statistically superior to placebo in regard to the Physician's Global Evaluation on all test days except Week 24 in Study 205.137. In regard to the total SGRQ scores, the difference between tiotropium and placebo did not reach the generally accepted threshold of a minimal clinically important difference (4 units) on any test day in either study.

SUMMARY OF BRONCHODILATOR EFFICACY RESULTS

Existing drugs for COPD are indicated for the relief of bronchospasm associated with COPD. As such, the standard for approval has been demonstration, through adequate and well-controlled trials, of a bronchodilator effect. The most commonly used index of bronchodilator effect has been the FEV₁. In most cases, the primary analyses of FEV₁ have focused on peak changes. In this application, the primary focus has been on the "trough FEV₁ response." This endpoint has the benefit of incorporating important information regarding end-of-dosing-interval bronchodilator efficacy. The limitation of this endpoint is that there is less experience and consensus regarding what constitutes a minimal clinically meaningful effect.

In the six Phase 3 studies submitted with this application, tiotropium has been consistently superior to placebo (or an active control that may be considered a proxy for placebo) in regard to the trough FEV₁ response. The treatment effect size on this endpoint, while less than what might be desired of a peak effect size, is likely clinically significant. Further, secondary analyses of serial spirometry during the early post-dosing period demonstrate that tiotropium is consistently superior to placebo in regard to peak and average FEV₁. Analyses of the mean peak FEV₁ values in the one-year, placebo-controlled studies suggest that the mean peak effect is clinically meaningful. It is interesting to note that the time to reach peak FEV₁ seems to vary substantially among individual subjects. Other secondary efficacy variables, such as home PEF values and supplemental "as-needed" albuterol use, also support the efficacy of tiotropium as a bronchodilator. No consistent effect was demonstrated on other indicators of COPD disease activity, such as COPD exacerbations, COPD hospitalizations, and health-related quality of life assessments.

LABELING ISSUES REGARDING BRONCHODILATOR EFFECT

The product labels for orally inhaled bronchodilators customarily provide information (text and figures) that describes the pharmacodynamic effect of the drug. Typical information that is conveyed includes peak effect, time to peak effect, and duration of action. For this drug, these concepts are not easy to convey. One difficulty is the fact that the bronchodilator effect is not

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(Studies 205.130 and 205.137). Supporting data may be drawn from other studies in which various indices of the symptom were captured as secondary endpoints. The following section of this Review will discuss the findings of Studies 205.130 and 205.137, along with this additional supporting data. The studies cited in the discussion are reviewed in depth in the Appendix to this document and summarized briefly above.

STUDIES 205.130 AND 205.137

In these six-month studies, which are summarized above and reviewed in-depth in the Appendix to this document, one of the co-primary variables was the Mahler Transition Dyspnea Index (TDI). The Applicant chose to specify as the primary analysis, a “responder” analysis based on a threshold of 1 unit in the focal TDI score. During drug development, the Agency informed the Applicant that the clinical validity of this threshold must be established in order for this primary analysis to be meaningful. Specifically, the Applicant was informed that it must establish that a TDI focal score of one is clinically meaningful. Further, the Applicant was informed that whatever effect was demonstrated in regard to the percentage of “responders” must itself be clinically meaningful in order to merit an indication for dyspnea associated with COPD.

At the end of the six-month studies, the percentages of patients with a TDI ≥ 1 unit was 42% and 45% in the tiotropium groups (Studies 205.130 and 205.137, respectively), compared with 26% and 33% in the placebo groups. These differences were statistically significant in both studies. The percentages of responders in the active-comparator group (salmeterol) was 35% and 48% in these two studies.

Percentage of Patients with TDI ≥ 1 After 6 Months of Treatment (Studies 205.130 and 205.137)			
Study	Tiotropium	Placebo	Salmeterol
205.130	42%	26%	35%
205.137	45%	33%	48%

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There are additional data from these two studies that may shed light on the effect of tiotropium in regard to the symptom of dyspnea. Because this would be a unique indication for tiotropium, some data on the effect of salmeterol on these endpoints is provided for comparison.

- Responder analyses for the TDI focal score (based on a threshold of 1 unit) were performed after 8 and 16 weeks of treatment. In both studies, tiotropium was statistically superior to placebo in these analyses. The percentages of responders in the tiotropium and placebo groups were 40% vs. 24% and 44% vs. 31% at Week 8, and 43% vs. 27% and 42% vs. 30% at Week 12 in Studies 205.130 and 205.137, respectively. Of note, in one study (205.130) tiotropium was numerically superior to salmeterol on these analyses, and in the other study (205.137), salmeterol was numerically superior to tiotropium.
- Using analyses of mean TDI focal scores rather than "responder" analyses, tiotropium was statistically superior to placebo on each test day in both studies. The effect size was >1 unit on each day except Week 16 in Study 205.130. Of note, in one study (205.130) salmeterol was not statistically superior to placebo on these analyses, but in the other study (205.137) salmeterol was statistically superior to placebo, with effect sizes ranging from 1.26 to 1.66.
- A "COPD Symptom Score," based on the investigator's assessment, was assigned at each treatment visit. Tiotropium was statistically superior to placebo in regard to the "shortness of breath" component of this score at most of the treatment visits. The effect size ranged from 0.17 to 0.36 on this 0-3 scale. Salmeterol was also statistically superior to placebo for "shortness of breath" at most treatment visits.
- A "shuttle walk test" (SWT) was administered after the first dose and after 8, 16, and 24 weeks of treatment. The "Modified Borg Dyspnea Scale" was administered before and after each SWT. In both studies, there was no difference between groups in regard to the distance walked in the SWT. Of note, in Study 205.137, on each test day the distance walked was numerically superior in the placebo group, as compared to the tiotropium group. There was no significant difference between tiotropium and placebo in regard to the Modified Borg scores. There was also no significant difference between salmeterol and placebo on the SWT distance or the Modified Borg score.

STUDIES 205.114/204.117 AND 205.115/205.128

In these studies, which are summarized above and reviewed in-depth in the Appendix to this document, the symptom of dyspnea was addressed in two secondary variables, the TDI and the component of the "COPD Symptoms Score" called "shortness of breath." The TDI was administered on five occasions during these 1-year studies. On all occasions the mean TDI focal score was statistically superior in the tiotropium group. However, the difference between the tiotropium and placebo group was <1 on all but three occasions. Symptoms of COPD were assessed and recorded by the investigator using a 0-3 scale at each visit. The tiotropium group was statistically superior to the placebo group in regard to the score on the "shortness of breath" component at most visits.

STUDIES 205.122A/205.126A AND 205.122B/205.126B

These active-controlled studies are summarized above and reviewed in-depth in the Appendix to this document. They TDI assessments on six occasions during the one-year treatment period. In Study 205.122A/205.126A, the tiotropium group was statistically superior to ipratropium in

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regard to the mean TDI focal score on four of the six occasions. However, the difference between the two groups was <0.75 units on each of these occasions. In Study 205.122B/205.126B, the tiotropium group was superior to ipratropium in regard to the mean TDI focal score on every occasion, with differences exceeding 1 unit on four of the six occasions.

STUDY 205.131

The study report for this study was submitted along with the 120-Day Safety Update. Aspects of this study relevant to the proposed dyspnea indication are discussed in-depth in the Appendix to this document. In this study, a total of 198 patients with COPD and lung hyperinflation were randomized to receive either tiotropium powder inhalation capsules (18mcg QD) or placebo for a six-week treatment period. During Visit 1, patients underwent a maximum exercise test to determine their maximal work capacity (Wcap). During Visits 2 and 3, patients underwent a constant workload exercise test at 75% of their Wcap. Patients were randomized to treatment at Visit 4. Constant workload exercise tests were repeated after the first dose of study medication (Visit 4) and after 3 and six weeks of treatment (Visits 5 and 6). The study also included numerous assessments of pulmonary function as well as subjective determinations of breathlessness and leg fatigue during exercise. The primary efficacy endpoint was the "endurance time" (exercise time, in minutes, during the constant workload exercise test) after six weeks of treatment. The pre-specified statistical model was an analysis of covariance with baseline (Visit 3) values used as covariates.

As discussed at length in the Appendix to this document, there was a marked difference between the two treatment groups in regard to the endurance time at Visit 3. Because Visit 3 served as the baseline visit for the pre-specified primary analysis, the results of this study are very difficult to interpret. The magnitude of the difference in endurance time at Visit 3 (49.8 seconds, placebo superior to active) approached that seen at Visit 6 (65.4 seconds, active superior to placebo).

Given the difficulty interpreting the primary efficacy endpoint, results of the secondary endpoints are considered inconclusive. A "responder" analysis of the TDI focal scores, based on a threshold of TDI focal score >0 , indicated that on Day 21 62% of the tiotropium patients and 30% of the placebo patients were "responders," and at Day 42 61% of the tiotropium patients and 34% of the placebo patients were "responders." The Modified Borg Dyspnea Score was assessed before the start of exercise, every two minutes during exercise, and at peak exercise. The specified statistical analysis was that the modified Borg scores would be analyzed by fitting the slopes over exercise time and over oxygen consumption (VO₂). The slopes were then to be analyzed by the same analysis of covariance model used for the primary analysis. During the two pre-treatment visits, the means for the modified Borg scores were higher in the tiotropium group at rest, at standardized exercise time, and at peak exercise. In the pre-specified analyses, tiotropium was not significantly different from placebo, with the exception of the ANCOVA analysis of the slope of the modified Borg score over time at Day 42 ($p=0.02$). At Day 0 and Day 21 there was no difference on this variable, and there was no difference in the ANCOVA of the slope of the modified Borg scores over VO₂.

SUMMARY OF THE DYSPNEA EFFICACY RESULTS

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The Applicant has proposed a unique indication for tiotropium, the treatment of dyspnea associated with COPD. The primary support for this proposal is derived from two, six-month, active and placebo-controlled studies in which the TDI, an index of subjective dyspnea, was pre-specified as one of two co-primary efficacy variables. In those studies, tiotropium was demonstrated to be statistically significantly superior to placebo in the pre-specified primary analysis. This analysis was a "responder" analysis using a threshold of 1 in the TDI as the definition of a "responder." The utility of this analysis will be discussed in the section below entitled Efficacy Conclusions. Secondary analyses including TDI responder analyses on other test days, and analyses of mean TDI focal score data also showed statistical superiority of tiotropium over placebo. It should be noted that in many of these analyses, the effect of tiotropium was not markedly greater than that of the active control, salmeterol. Finally, in these studies, no difference between groups was seen in regard to the distance walked during a shuttle walk test, or perceived dyspnea during the shuttle walk test, as assessed by the modified Borg scale.

In other long-term, placebo controlled studies, the TDI data was analyzed using mean values. While tiotropium was often statistically superior to its comparator (placebo or ipratropium), the differences were commonly <1 unit. The Applicant also submitted a six-week exercise study in support of the proposed dyspnea indication. However, the data from that study are difficult to interpret due to differences between treatment groups at baseline.

D. Efficacy Conclusions

The clinical development program for this drug included a total of six large, controlled studies in patients with COPD. Of these, two were 1-year, placebo-controlled studies, two were 1-year, active (ipratropium)-controlled studies, and two were 6-month, active (salmeterol)- and placebo-controlled studies. The one-year studies primarily focused on establishing substantial evidence of efficacy to support the indication traditionally used for COPD drugs, the relief of bronchospasm associated with COPD. Thus, in these studies the primary efficacy variable was a measure of bronchodilation, FEV₁. One unique aspect of these studies is that the primary endpoint was the pre-dose FEV₁, rather than a post-dose assessment, such as peak FEV₁, as is more commonly used. The benefit of using the pre-dose (or "trough") value is that by showing statistical superiority to the comparator, the proposed dosing interval is supported. However, there is less of a consensus regarding the minimum magnitude of effect that should be regarded as being clinically meaningful at this timepoint.

The 6-month studies were submitted in order to support a proposal for a unique indication for a COPD drug, the treatment of dyspnea associated with COPD. Prior to unblinding the data for these studies, the primary efficacy variable for these studies was altered, to include FEV₁ and TDI focal score as co-primary variables. The following discussion will address the proposed indications, treatment of bronchospasm associated with COPD and treatment of dyspnea associated with COPD, separately.

The six clinical studies successfully established the bronchodilator efficacy of tiotropium. Primary analyses of the six studies all demonstrate that treatment with tiotropium at the proposed

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dose results in statistically significant improvements in FEV₁ at the end of the dosing interval ("trough" FEV₁). In four of the studies the comparator was placebo, and in the remaining two studies the comparator was a short-acting agent whose effect is expected to be negligible at the time the variable was assessed (morning, pre-dose). The magnitude of effect demonstrated is considered to be clinically meaningful. In addition, secondary analyses of the FEV₁ data established that tiotropium is significantly superior to placebo in regard to standard post-dose variables such as average FEV₁ and peak FEV₁. It is noted that the time to reach peak FEV₁ is quite variable among individual patients. Finally, other secondary efficacy variables, such as morning and evening home peak flow measurements and supplemental "as-needed" albuterol use, also support the efficacy of tiotropium as a bronchodilator in COPD patients. No consistent effect was seen on other indicators of COPD disease activity, such as COPD exacerbations, COPD hospitalizations, and health-related quality of life assessments.

The support of a proposed "dyspnea" indication is less convincing. It is true that in the two six-month studies tiotropium was statistically superior to placebo on the co-primary analysis of the TDI focal score. However, several points regarding the TDI analysis should be noted.

- First, the applicant did not submit any details regarding the development of the TDI instrument. It is not clear from the submission that appropriate methodology was used to develop the instrument. Appropriate development of a patient reported outcome instrument typically involves: 1) convening of "focus groups" of the specific patient population in order to identify items of importance, 2) reducing the number of these items in order to eliminate highly correlated items, 3) determining the most appropriate response choices, and 4) assigning the most appropriate weight to each item.
- Second, there is limited validation in the literature for the use of the TDI focal score in studies of extended duration (e.g. 6-12 months). Responses to the TDI involve recollection of the baseline status, which may be difficult after many months. For instance, the baseline assessment of "Magnitude of Task" is determined in the Baseline Dyspnea Index (BDI) using four Grades of severity. A score +1 on the TDI for this category, represents an improvement of less than one grade. The ability of patients to make a determination of a change within one grade after 6 or 12 months is not clear.
- Third, there is little consensus in the medical literature regarding the minimal TDI focal score that is considered to be clinically meaningful. Therefore the selection of the most appropriate "responder" threshold is somewhat uncertain. The Applicant has proposed that 1 unit is clinically meaningful. It should be noted that this also represents the smallest improvement that a patient could possibly report. This means that there is no degree of improvement that could be reported that would not be considered to be clinically meaningful. Of note, however, according to analyses performed by the Division's Biometrics Reviewer, tiotropium would have been statistically superior to placebo in the two 6-month studies even if the "responder" threshold were set at 2, rather than 1. Using a response threshold of 2, the percentage of responders in the tiotropium and placebo groups was 33.7% and 23% in Study 205.130, and 40.8% and 29.8% in Study 205.137. For comparison, the using this threshold, the percentage of responders in the salmeterol groups was 30.7% and 46.6% in Study 205.130 and 205.137, respectively.
- Fourth, the six-month studies were multinational. The Applicant has not provided data to establish the validity of the TDI when translated into languages other than English.

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- Fifth, the effect size demonstrated was not sufficient to merit a specific indication for dyspnea. In one study 42% of tiotropium patients were classified as “responders,” while 26% of placebo patients were “responders.” In the second study, the difference between the groups was even smaller (45% vs. 33%). According to “number needed to treat” (NNT) analyses performed by the Division’s Biometrics Reviewer, approximately 7.5 patients would need to be treated with tiotropium in order that one patient would note a dyspnea benefit above that expected with the use of placebo. (This figure is derived from the pooled data from the two studies. The NNT was 6.45 in Study 205.130, and 8.6 from Study 205.137).
- Sixth, the robustness of the dyspnea effect is called into question by the fact that in analyses of mean TDI focal scores in the pivotal studies the difference between tiotropium and placebo was often less than 1 unit.
- Finally, the comparator drug used in the two six-month studies (salmeterol) does not have an indication for dyspnea, yet its performance in the “responder” analyses was not different from that of tiotropium. The Biometrics Team Leader has undertaken a detailed review of the existing validation for the TDI, as used in this study. That review is contained in a separate document.

On September 6, 2002, the Pulmonary-Allergy Drugs Advisory Committee (PADAC) met to discuss this Application. The PADAC concluded that the data provided substantial and convincing evidence that tiotropium provides a clinically meaningful bronchodilator effect in patients with COPD. They also concluded that the data did not provide substantial and convincing evidence that the drug provides a clinically meaningful effect for the symptom of dyspnea.

In summary, the evidence of efficacy in regard to a bronchodilator effect is adequate to support approval. However, the evidence of a robust, clinically meaningful benefit in regard to dyspnea associated with COPD is not sufficient to merit an indication for dyspnea.

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VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The clinical development program included adequate numbers of subjects exposed. The types of safety assessments used in these studies was adequate, and was generally consistent with development programs for other inhalation drug products for a COPD indication. The adverse event data indicated that anticholinergic effects were more frequent in the treated group. Dry mouth was quite common, and was more frequent in women and in older patients. Other anticholinergic effects included constipation and urinary effects. Upper respiratory tract infections were also more common in the tiotropium-treated patients. The safety database also contains subtle suggestions that tiotropium may be associated with increased adverse cardiac effects, particularly in the category of "heart rate and rhythm disorders." The cardiac safety database contains relatively few 24-hour Holter monitors. Given the potential, based on mechanism of action, pharmacokinetics, and intended patient population, for adverse cardiac effects with this drug, additional Holter data should be pursued as a Phase 4 commitment.

B. Description of Patient Exposure

1. *Clinical Studies*

The Phase 3 development program included six "pivotal" clinical studies. Four of these were randomized, double-blind, active- or placebo-controlled studies with treatment durations of approximately one year. These studies were conducted in the U.S., Netherlands, and Belgium. The two remaining studies were randomized, double-blind, active and placebo-controlled studies with treatment durations of six months. Three additional studies are described by the Applicant as Phase 3 "characterization" studies. These were: 1) a six-week placebo-controlled study comparing morning to evening dosing ("AM/PM dosing study"; 205.123); 2) a mucociliary clearance study (205.116); and 3) a sleep study (205.124).

Additional clinical studies include eleven human pharmacology studies, three Phase 2 single-dose studies (205.119, 205.120, and 205.139), one Phase 2 multiple-dose, dose ranging study (205.108), one multiple-dose dose-ranging study using tiotropium inhalation solution and inhalation powder, and four studies in patients with asthma.

This Medical Officer Review will focus primarily on safety data derived from the six "pivotal" clinical studies. Following the approach taken by the Applicant in the Applicant's Integrated Summary of Safety, the pooled safety data from the two 1-year placebo controlled studies, the pooled safety data from the two 1-year ipratropium-controlled studies, and the pooled safety data from the two 6-month salmeterol and placebo-controlled studies will be discussed separately. Additional relevant safety information from the remainder of the clinical studies will be discussed as well.

2. *Exposure*

A total of 4,124 subjects participated in the clinical program [iss.pdf/p102]. This included 224 healthy volunteers, 3,411 COPD patients, 471 asthma patients, and 18 patients with renal

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impairment. A total of 2,117 subjects were exposed to tiotropium by inhalation of the powder capsule formulation. This included 57 healthy volunteers, 1,723 COPD patients, and 337 asthma patients. A total of 1,701 subjects were exposed to the 18mcg dose of tiotropium. Of these 1,701 subjects, 48% were exposed to the drug for more than 200 days, and 34% were exposed to the drug for more than 330 days.

The table below summarizes the numbers of patients exposed to tiotropium in the six “pivotal” Phase 3 studies.

Patient Exposure to Tiotropium in the Six “Pivotal” Phase 3 Studies				[iss.pdf/p113-4]
	Total	≥101 days	≥200 days	≥ 330 days
One-year, placebo-controlled studies	550	501 (91%)	482 (88%)	302 (55%)
One-year, ipratropium-controlled studies	356	325 (91%)	316 (89%)	260 (73%)
Six-month, salmeterol- and placebo-controlled studies	402	353 (88%)	354 (88%)	not applicable

The mean age for all patients was 65 years in the one-year placebo-controlled studies, and 64 years in the one-year ipratropium-controlled studies and the six-month salmeterol and placebo-controlled studies. Nearly all patients were caucasian, and 65% to 85% were male [iss.pdf/p127, 133]. In the one-year, placebo-controlled studies, the mean FEV₁ was approximately 1 liter, representing 38-39% of the predicted value. In the one-year, ipratropium-controlled studies the mean baseline FEV₁ was 1.18 to 1.25 liters, representing 41-44% of the predicted value [iss.pdf/p129]. In the six-month, salmeterol- and placebo-controlled studies the mean baseline FEV₁ was 1.07 to 1.12 liters, representing 39-41% of the predicted value [iss.pdf/p134].

C. Methods and Specific Findings of Safety Review

1. Safety Evaluations Performed

In the tiotropium clinical studies safety was monitored using the following assessments: clinical adverse events, vital signs, physical examinations, clinical laboratory results, and electrocardiograms (ECGs). Adverse events were classified using the Boehringer Ingelheim – World Health Organization – Adverse Reaction Terminology List (BI-WHO-ART) [iss.pdf/p82]. The respiratory system events were further divided into “upper” and “lower” respiratory system disorders. One of the (non-pivotal) clinical studies included 24-hour Holter monitoring (Study 205.123, one of the Phase 3 “characterization” studies).

2. Significant/Potentially Significant Events (Deaths, Serious Adverse Events, and Discontinuations Due to Adverse Events)

The table below summarizes the incidences of deaths, serious adverse events (SAEs), and adverse events leading to discontinuation in the three sets of “pivotal” Phase 3 studies.

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Significant/ Potentially Significant Adverse Event Profile														[iss.pdf/p33, 44]
	1-year, placebo-controlled studies				1-year, ipratropium-controlled studies				6-month, salmeterol and placebo-controlled studies					
	Tiotropium		Placebo		Tiotropium		Ipratropium		Tiotropium		Salmeterol		Placebo	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total Treated	550	100	371	100	356	100	179	100	402	100	405	100	400	100
Deaths	7	1.3	7	1.9	9	2.5	3	1.7	1	0.2	6	1.5	5	1.3
SAEs	99	18	78	21	57	16	46	25.7	37	9.2	50	12.3	55	13.8
AEs leading to discontinuation	53	9.6	50	13.5	35	9.8	22	12.3	29	7.2	60	14.8	64	16.0

A total of 26 deaths occurred among the 1456 patients enrolled in the one-year studies [iss.pdf/p145]. None of the deaths were considered by the investigators to be related to study medication. In general, the causes of death were consistent with what might be expected in this patient population. Two causes of death were reported in the tiotropium groups but not in the comparator groups. These were myocardial infarction (4 deaths) and arrhythmia (1 death). The incidence of death was similar in all groups. In the one-year, placebo-controlled studies, there were 7 (1.3%) deaths in the tiotropium group and 7 (1.9%) in the placebo group. In the one-year, ipratropium-controlled studies there were 9 (2.5%) deaths in the tiotropium and 3 (1.7%) deaths in the ipratropium group. Narrative summaries of all deaths were reviewed by the Medical Reviewer.

The seven deaths among the tiotropium patients in the one-year, placebo-controlled studies were due to [iss.pdf/p149-54]:

- acute myocardial infarction:
 - 67 year-old man, after 227 days of treatment.
- coronary artery disease
 - 49 year-old man developed severe chest pain after 91 days of treatment. Cardiac catheterization revealed single vessel disease (60% lesion). Cardiac medications were begun during a seven day hospitalization, but twelve days later he developed recurrent chest pain and expired.
- cardiac arrhythmia:
 - 85 year-old man found dead after 33 days of treatment. No autopsy.
- sudden death:
 - 59 year-old man found dead in bed after 45 days of treatment.
- cardiac arrest:
 - 61 year-old man with history of hypertension and coronary artery disease (status post coronary artery bypass grafting) experienced cardiac arrest after 15 days of treatment. He was initially resuscitated and placed on a ventilator, but died two days later.
- congestive heart failure/ cardiomyopathy:
 - 65 year-old woman with a baseline diagnosis of cardiomyopathy, who was hospitalized for congestive heart failure after 339 days of treatment. She was hospitalized for 15 days for diagnostic testing and treatment. She was readmitted 5 days later with congestive heart failure, and died.
- suicide:

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- 51 year-old man with history of post-traumatic stress disorder died of suicide (opiate, cocaine, and diphenhydramine intoxication) after 112 days of treatment.

Thus, five of these seven deaths among the tiotropium patients in the one-year, placebo-controlled trials were attributable to cardiac ischemia or arrhythmia. For comparison, only one of the seven deaths in the placebo group was attributed to cardiac ischemia or arrhythmia. (This was a 65 year-old man with a history of hypertension who died after 240 days of treatment. Details of the circumstances of his death are not provided, but an autopsy revealed atherosclerotic coronary disease without signs of acute myocardial infarction.) The remaining deaths in the placebo group were due to worsening COPD (1 patient), cor pulmonale (1 patient; recorded as "myocardial insufficiency"), and carcinoma (4 patients).

In the one-year, ipratropium-controlled studies there were two deaths in the tiotropium group (out of a total of 7) due to myocardial infarction, and no deaths in the ipratropium group (out of a total of 3) due to myocardial infarction [iss.pdf/p154-9]. The remaining causes of death were carcinoma, pulmonary emboli, respiratory insufficiency, and meningitis in the tiotropium group, and pneumonia, aortic aneurysm rupture, and carcinoma (with treatment-related leukopenia and sepsis) in the ipratropium group.

In the six-month studies there was only one death in the tiotropium group. This was due to ruptured abdominal aortic aneurysm [iss.pdf/p183]. For comparison, there were five deaths in the placebo groups of the six-month studies. These deaths were due to cardiac arrest (two events, one of which occurred in association with COPD exacerbation), respiratory insufficiency, bronchial carcinoma, and "death" (patient was found dead, cause not specified) [iss.pdf/p184-8].

Fewer patients in the tiotropium groups reported serious adverse events, as compared with both the placebo and the active comparator groups. As indicated in the table above, the percent of patients reporting SAEs in the tiotropium group was 18% in the one-year, placebo-controlled studies and 16% in the one-year, ipratropium-controlled studies, compared with 21% of placebo patients and 26% of ipratropium patients [iss.pdf/p159]. In the six-month studies, 9.2% of tiotropium patients, 14% of placebo patients, and 12% of salmeterol patients reported SAEs.

The most common SAEs were COPD exacerbation and pneumonia. None of the SAEs were considered to be related to tiotropium. COPD exacerbation SAEs were less common in the tiotropium groups (5.8% vs. 8.1% in the placebo-controlled one-year studies, 6.5% vs. 12% in the ipratropium controlled studies, and 3.5% vs. 5.8% in the placebo group and 5.9% in the salmeterol group in the 6-month studies) [iss.pdf/p39, 47]. The table below indicates the SAEs that occurred in >1 patient in the tiotropium group and occurred more frequently in the tiotropium group in the one-year, placebo-controlled studies.

Serious Adverse Events Occurring More Frequently in the Tiotropium Group And Occurring in >1 Patient in the Tiotropium Group (One-year, Placebo-Controlled Studies) (number [%] of patients) [iss.pdf/p161-6]		
Event	Tiotropium Group	Placebo Group
Chest Pain	8 (1.5)	4 (1.1)
Dehydration	5 (0.9)	0 (0)

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Serious Adverse Events Occurring More Frequently in the Tiotropium Group And Occurring in >1 Patient in the Tiotropium Group (One-year, Placebo-Controlled Studies) (number [%] of patients) [iss.pdf/p161-6]		
Event	Tiotropium Group	Placebo Group
Neoplasm Malignant	4 (0.7)	0 (0)
Syncope	3 (0.5)	0 (0)
Myocardial Infarction	3 (0.5)	1 (0.3)
Angina Pectoris	2 (0.4)	1 (0.3)
Fibrillation, Atrial	2 (0.4)	1 (0.3)
Prostatic Disorder	2 (0.4)	0 (0)
Diabetes Mellitus, Aggravated	2 (0.4)	0 (0)
Hyperglycemia	2 (0.4)	0 (0)
Accident, Vehicular	2 (0.4)	0 (0)
Manic Reaction	2 (0.4)	0 (0)
Infection	2 (0.4)	0 (0)

As shown in the table above the SAEs that occurred in the tiotropium group but did not occur in the placebo group in the one-year, placebo-controlled studies were: dehydration (5 events), syncope (3 events), prostatic disorder (2 events), vehicular accident (2 events), diabetes mellitus aggravated (2 events), hyperglycemia (2 events), manic reaction (2 events), and infection (2 events). In addition, one event of each of the following occurred in the tiotropium group, but did not occur in the placebo group: allergic reaction, arrhythmia, cardiac arrest, angina pectoris aggravated, coronary thrombus, sick sinus syndrome, tachycardia, tachycardia supraventricular, aneurysm, aortic stenosis, cardiomyopathy, hemoptysis, hypoxia, sinusitis, constipation, ileus, colitis, dysphagia, gastrointestinal disorder NOS, gastroesophageal reflux, esophagitis, goiter, hyperkalemia, colon carcinoma, larynx neoplasm malignant, malignant melanoma, neoplasm malignant, uterine carcinoma, neuritis, anxiety, delirium, depression, suicide attempt, cerebellar infarction, thrombus arterial leg, lymphadenopathy, herpes zoster, hydronephrosis, and renal calculus [iss.pdf/p161-6].

In the six-month studies, SAEs occurring in the tiotropium group but not in the placebo group were: upper respiratory tract infection (2 events), gastroenteritis (2 events), and one episode each of the following: tachycardia supraventricular, skeletal pain, aneurysm, breast neoplasm malignant (female), epididymitis, prostatic disorder, testis disorder, abdomen enlarged, accident household, cor pulmonale, arthritis rheumatoid aggravated, duodenal ulcer, skin ulceration, urticaria, epistaxis, and cataract [iss.pdf/p191-3].

The incidence of discontinuation due to adverse events was lower in the tiotropium groups as compared with both the placebo and the active comparator groups. In the one-year, placebo-controlled studies, 53 (9.6%) of tiotropium patients and 50 (14%) of placebo patients discontinued due to an adverse event [iss.pdf/p167]. In those studies, events leading to discontinuation that were seen in more than two patients in a treatment group are listed in the table below. Dry mouth, the only event that occurred more frequently in the tiotropium group, is shaded.

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Adverse Events Leading to Discontinuation, occurring in more than 2 patients in the one-year, placebo-controlled studies (number [%] of patients) [iss.pdf/p167]		
Event	Tiotropium Group	Placebo Group
COPD Exacerbation	20 (3.6%)	19 (5.1%)
Dyspnea	0 (0%)	5 (1.3%)
Pneumonia	4 (0.7%)	5 (1.3%)
Cardiac Failure	2 (0.4%)	3 (0.8%)
Dry Mouth	3 (0.5%)	1 (0.3%)

In the 6-month studies, 7.2% of tiotropium patients and 16% of placebo patients discontinued due to an adverse event [iss.pdf/p194]. In these studies, COPD exacerbation and dyspnea were the only AEs that led to discontinuation of more than 2 patients in a treatment group. COPD exacerbation was the cause of discontinuation in 3.5% of tiotropium patients and 7.5% of placebo patients, and dyspnea was the cause of discontinuation in 1.2% of tiotropium patients and 3.3% of placebo patients. Dry mouth led to discontinuation in 1 tiotropium patient (0.2%) and in 0 patients in the placebo and salmeterol groups.

3. Other Safety Findings: Adverse Events, Lab Findings, Vital Signs, and ECGs

The table below summarizes the overall incidence of adverse events and the incidence of those adverse events that were considered by the investigator to be possibly drug-related. The overall incidence of adverse events was similar among the groups. Of note, the incidence of drug-related adverse events was greater in the tiotropium group, as compared to placebo and as compared to each of the active comparators examined (ipratropium and salmeterol). This is due to the increased incidence of drug-related dry mouth with tiotropium.

Adverse Event Profile [iss.pdf/p33, 44]														
	1-year, placebo-controlled studies				1-year, ipratropium-controlled studies				6-month, salmeterol and placebo-controlled studies					
	Tiotropium		Placebo		Tiotropium		Ipratropium		Tiotropium		Salmeterol		Placebo	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total Treated	550	100	371	100	356	100	179	100	402	100	405	100	400	100
All Adverse Events	495	90	338	91.1	318	89.3	162	90.5	298	74.1	305	75.3	307	76.8
Drug-related Adverse Events	104	18.9	34	9.2	73	20.5	22	12.3	44	10.9	33	8.1	31	7.8

The tables below summarize adverse events that were reported by $\geq 3\%$ of patients in the tiotropium group and occurred more frequently in the tiotropium group as compared to the placebo group. For purposes of reference, the tables contain data on the incidence of these AEs in the active comparator groups. The active comparator data is drawn from separate studies in the case of the one-year studies, and from the same studies in the case of the 6-month studies. The first table contains the one-year studies, and the second table contains the 6-month studies.

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Adverse Events Reported by $\geq 3\%$ of Patients in the Tiotropium Group and Occurring More Frequently in the Tiotropium Group as Compared with the Placebo Group [One-Year Studies] [iss.pdf/p143-4]									
		1-year, placebo-controlled studies				1-year, ipratropium-controlled studies			
		Tiotropium		Placebo		Tiotropium		Ipratropium	
		N	(%)	N	(%)	N	(%)	N	(%)
Total Treated		550	100	371	100	356	100	179	100
Body as a Whole									
	Accidents	73	13.3	42	11.3	16	4.5	14	7.8
	Chest Pain	38	6.9	17	4.6	19	5.3	4	2.2
	Edema, dependent	25	4.5	13	3.5	10	2.8	9	5.0
	Influenza-Like Symptoms	45	8.2	30	8.1	39	11.0	25	14.0
Gastrointestinal System									
	Abdominal Pain	26	4.7	11	3.0	20	5.6	11	6.1
	Constipation	19	3.5	6	1.6	2	0.6	2	1.1
	Dyspepsia	32	5.8	17	4.6	5	1.4	1	0.6
	Mouth Dry	88	16.0	10	2.7	43	12.1	11	6.1
	Vomiting	19	3.5	9	2.4	3	0.8	3	1.7
Musculoskeletal System									
	Arthritis	26	4.7	17	4.6	15	4.2	7	3.9
	Myalgia	21	3.8	11	3.0	13	3.7	6	3.4
Resistance Mechanism Disorders									
	Infection	23	4.2	12	3.2	5	1.4	5	2.8
	Moniliasis	20	3.6	9	2.4	10	2.8	3	1.7
Respiratory System									
	Coughing	26	4.7	17	4.6	30	8.4	17	9.5
	Epistaxis	20	3.6	7	1.9	4	1.1	2	1.1
	Pharyngitis	49	8.9	27	7.3	23	6.5	5	2.8
	Rhinitis	30	5.5	20	5.4	9	2.5	4	2.2
	Sinusitis	62	11.3	35	9.4	12	3.4	4	2.2
	Upper Respiratory Tract Infection	226	41.1	138	37.2	153	43.0	62	34.6
Skin and Appendages									
	Rash	23	4.2	8	2.2	7	2.0	4	2.2
Urinary System									
	Urinary Tract Infection	40	7.3	19	5.1	14	3.9	4	2.2

In the one-year placebo-controlled studies, the most notable adverse events were related to the gastrointestinal system (abdominal pain, constipation, dyspepsia, dry mouth, and vomiting). The occurrence of AEs in the category of "Gastrointestinal System Disorders" was 38.5% in the tiotropium group and 29.1% in the placebo group [issa.pdf/13]. Of these, by far the most common was dry mouth, with an incidence of 16% in the tiotropium group. Of note, the one-year ipratropium-controlled studies demonstrated that the frequency of dry mouth is greater with tiotropium than with the related drug, ipratropium. Upper respiratory tract infections were also remarkably more common in the tiotropium groups as compared to both the placebo group and the ipratropium group. Other upper respiratory tract AEs, such as epistaxis, pharyngitis, and sinusitis may reflect drying effects of this anticholinergic compound on the airway mucosa. The mechanism that might be responsible for the observed increased incidence of urinary tract infections in the tiotropium group is not known, but may relate to urinary stasis due to anticholinergic effects on the genitourinary system.

The table above includes adverse events reported by $\geq 3\%$ of subjects in a treatment group. The listings of all AEs reported in the one-year, placebo-controlled studies, by treatment group, were reviewed [issa.pdf/p7-34]. The following observations are derived from these listings:

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- The AE “allergic reaction” occurred in 14 (2.5%) patients in the tiotropium group and 3 (0.8%) patients in the placebo group.
- The AE “tooth caries” occurred in 4 (0.7%) patients in the tiotropium group and 0 patients in the placebo group.
- The occurrence of AEs in the category “Metabolic and Nutritional Disorders” was 6.4% in the tiotropium group and 2.7% in the placebo group. This difference is primarily the result of the following disparities in the occurrence of AEs in this category:
 - 1) “diabetes mellitus”, “diabetes mellitus aggravated,” or “hyperglycemia” was reported in 14 (2.5%) tiotropium patients and was reported in only 1 (0.3%) placebo patients;
 - 2) “dehydration” was reported in five tiotropium patients (0.9%) and was not reported in any placebo patients; **Reviewer’s Comment: It is not clear if the occurrence of dehydration was related to the reported hyperglycemia/diabetes.**
 - 3) “hypercholesterolemia” was reported in 6 (1.1%) tiotropium patients and 1 (0.3%) placebo patients.
- “Urinary retention” occurred in 4 (0.7%) tiotropium patients and 0 placebo patients.
- “Micturation disorder” or “micturation frequency” occurred in 6 (1.1%) tiotropium patients and 0 placebo patients.

Reviewer’s Note: With the exception of hypercholesterolemia, which was slightly more common in the tiotropium group than the placebo group (1.0% vs. 0.3%), the adverse event data from the six-month studies did not confirm these observations [issa.pdf/p201-22].

Adverse Events Reported by ≥3% of Patients in the Tiotropium Group and Occurring More Frequently in the Tiotropium Group as Compared with the Placebo Group [6-month Studies] [iss.pdf/p182]						
	Tiotropium		Placebo		Salmeterol	
	N	(%)	N	(%)	N	(%)
Total Treated	402	100	400	100	405	100
Body as a Whole						
Accidents	17	4.2	10	2.5	21	5.2
Back Pain	16	4.0	12	3.0	16	4.0
Chest Pain	16	4.0	15	3.8	14	3.5
Influenza-Like Symptoms	27	6.7	16	4.0	21	5.2
Gastrointestinal System						
Mouth Dry	33	8.2	9	2.3	7	1.7
Respiratory System						
Pharyngitis	18	4.5	12	3.0	14	3.5
Sinusitis	13	3.2	10	2.5	1	0.2
Upper Respiratory Tract Infection	78	19.4	64	16.0	69	17.0

The AE data from the 6-month studies indicate fewer differences between tiotropium and placebo. Several of the AEs that were more common in the tiotropium group in the 1-year studies were also noted to be more common in the tiotropium group in the 6-month studies. Most notable among these were dry mouth, upper respiratory tract infection, influenza-like symptoms, and pharyngitis.

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In these studies, the investigators were asked to indicate which adverse events were considered to be possibly related to study drug. The most common adverse event that was considered to be possibly drug related was dry mouth [iss.pdf/p37-8, 46-7]. Drug-related dry mouth was reported in 14% of the tiotropium patients in the placebo-controlled studies (compared with 2.2% of placebo patients), in 11% of tiotropium patients in the ipratropium-controlled studies (compared with 5.6% of ipratropium patients), and in 6.5% of tiotropium patients in the 6-month studies (compared with 1% in the placebo and the salmeterol patients). Drug-related dysphonia was also more common in the tiotropium group as compared with placebo in the one-year studies (1.5% vs. 0.3%), but not in the 6-month studies. Finally, drug-related pharyngitis was slightly more common in the tiotropium group (1.1% vs. 0.8% in the placebo-controlled studies, and 1.1% vs. 0% in the ipratropium-controlled studies) in the one-year studies.

Vital signs were measured at the screening visit and on test days at the same intervals as the pulmonary function testing for the first three hours post dose (vital signs were measured just prior to pulmonary function measurements) [iss.pdf/p82]. The mean values for heart rate and blood pressure were similar in the tiotropium and the placebo groups [issa.pdf/p263-5]. The Applicant defined "marked changes" in vital signs as follows [iss.pdf/p229]:

- Systolic BP increase: an increase of ≥ 25 mmHg above baseline
- Systolic BP decrease: below 100mmHg if not at that level at baseline, and a decrease of greater than 10mmHg below baseline
- Diastolic BP increase: above 90mmHg and an increase of greater than 10mmHg from baseline
- Diastolic BP decrease: below 60mmHg if not at that level at baseline and a decrease of >10 mmHg below baseline
- Pulse increase: greater than 100bpm if not at that level at baseline and an increase of $>10\%$ above baseline.
- Pulse decrease: below 60bpm if not at that level at baseline and a decrease of >10 bpm below baseline

The incidence of "marked changes" from baseline (as defined by the Applicant) were generally similar in the tiotropium and placebo groups [iss.pdf/p236-7]. On Test Day 1 in the one-year, placebo-controlled studies, more patients in the tiotropium group developed a marked decrease in systolic blood pressure (defined as: below 100mm Hg if not at that level at baseline, and a decrease of greater than 10mm Hg below baseline [iss.pdf/p229]), as compared with placebo (3.1% vs. 0.5%). Because patients with potentially significant changes in pulse rate due to the anticholinergic effects of the drug might not be captured by the definition of a "marked change" for increased pulse, the Applicant was asked to submit shift tables for pulse rate increases of various magnitudes. This data was submitted on July 31, 2002. In all of the placebo-controlled studies, no remarkable difference was seen between tiotropium and placebo in regard to the percentages of patients who exhibited increases in heart rates of >5 , >10 , >15 , or >20 beats per minute at any test day [Submission dated 7/31/02, pages 4-9].

In the four 1-year Phase 3 studies, laboratory testing was performed at baseline and at three-month intervals throughout the treatment period [iss.pdf/p83]. In the two 6-month Phase 3 studies, laboratory testing was performed at baseline and at the end of the study. Laboratory

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tests included hematology, clinical chemistry, and urinalysis. The mean values for all parameters both at baseline and conclusion of patient participation were similar between treatment groups [iss.pdf/p244-50]. The incidence of "marked" changes in laboratory values (as defined by the Applicant) from baseline to final evaluation was similar among groups in the one-year and the six-month studies [iss.pdf/p251-6]. In the one-year, ipratropium-controlled studies there was a relatively high percentage of subjects in each group who demonstrated "marked" increase in LDH (12.7% in the tiotropium group and 9.9% in the ipratropium group). Marked elevations in other liver enzymes were not seen, nor were marked changes in hemoglobin or hematocrit to suggest hemolysis as a source of the LDH.

In the one-year, placebo-controlled studies there was no difference between groups in the percentage of patients with clinically significant changes in physical examination (defined by the Applicant) from baseline to final examination. In the one-year, placebo-controlled studies there were 46 (8.4%) such patients in the tiotropium group and 36 (9.7%) such patients in the placebo group [iss.pdf/p257].

Electrocardiogram data are discussed in the section below, entitled "Adverse Events Related to the Pharmacologic Actions of the Drug."

Paradoxical bronchospasm, defined as a decline in FEV₁ by at least 15% from baseline within 30 minutes of administration of study drug, was less frequent in the tiotropium group than in the placebo group in the one-year, placebo-controlled studies (4.5% vs. 12%) [iss.pdf/p240]. In five of the 25 tiotropium patients who exhibited paradoxical bronchospasm, the event occurred on two test days. In the one-year, ipratropium-controlled studies 15 (4.2%) patients in the tiotropium group and 1 (0.6%) patient in the ipratropium group experienced paradoxical bronchospasm. In the six-month studies 10 (1.0%) patients in the tiotropium group, 22 (2.1%) patients in the salmeterol group, and 33 (3.2%) patients in the placebo group experienced paradoxical bronchospasm. There were no discontinuations of tiotropium due to paradoxical bronchospasm.

4. Pregnancy

No pregnancies were reported during the conduct of any of the clinical studies for tiotropium [Submission date 7/24/02, page 4].

5. Interactions

Drug-Demographic Interactions

In order to assess the effect of age on the safety of tiotropium, adverse events were analyzed according to age groups (≤ 60 years, 61-70 years, and ≥ 71 years) [iss.pdf/p41]. In the one-year placebo-controlled studies, two specific adverse events were noted to occur with increasing frequency in the older age groups in the tiotropium group only, suggesting a drug-age interaction. These were dry mouth, and constipation. A third AE, urinary tract infection, occurred with greater frequency in older patients in both treatment arms, although the effect was more marked in the tiotropium group.

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The adverse event "dry mouth" increased in frequency with age in the tiotropium group. In the one-year, placebo-controlled studies the percent of patients with dry mouth was 11% in the younger age group, 16% in the middle age group, and 21% in the older age group [iss.pdf/p176]. In contrast, the incidence of this adverse event in the placebo group was 3.0%, 1.9%, and 3.5% in the three age groups. This observation was also made in the one-year, ipratropium-controlled studies, in which the percentages of patients with dry mouth also increased with age (7.7%, 15%, and 14%). In contrast, the percentages declined with age in the ipratropium group (8.2%, 6.1%, and 4.2%) in these studies [iss.pdf/p41]. Drug-age interaction was not suggested in the 6-month studies [iss.pdf/p49].

In the one-year, placebo-controlled studies constipation was also more frequent with increasing age in the tiotropium group (2%, 2.8%, and 6%), but not in the placebo group (3.0%, 0.6%, and 1.7%). In these studies, urinary tract infection occurred with increased frequency in the older age groups in the both the tiotropium group (3.3%, 5.2%, and 12%), and the placebo group (2.0%, 3.9%, and 6.1%), although the frequency was greater in the tiotropium group. These observations were not made in the one-year, ipratropium-controlled studies or the six-month studies [iss.pdf/p49].

Reviewer's Comment: The observation that dry mouth, constipation, and urinary tract infection occur more frequently with increasing age in the tiotropium group, along with the observation of increased systemic drug exposure with increasing age (see discussion of pharmacokinetics in Section III of this Medical Officer Review) suggest that these adverse events represent systemic effects of the drug.

The majority of patients in the pivotal clinical studies were men. The proportions of patients with adverse events was generally similar between genders within each treatment group, with the exception of dry mouth. In the one-year, placebo-controlled studies the frequency of dry mouth in the tiotropium group was 23% among women, and 13% among men. For comparison, the frequencies in the placebo group were 2.9% in women and 2.6% in men [iss.pdf/p177]. This pattern was also seen in the six-month studies, with dry mouth being reported by 14.3% of women and 6.4% of men [iss.pdf/p49]. In the one-year, ipratropium-controlled studies women also reported more dry mouth than men [iss.pdf/p42].

Genitourinary effects also showed evidence of a gender effect in the one-year studies. The adverse events "urinary retention" and "micturation disorder" were reported solely in men, and there was an increase in the frequency of urinary tract infection among men. Urinary retention occurred only in men in the tiotropium group (1.1%) in the one-year, placebo-controlled studies. Micturation disorders occurred only in men receiving either tiotropium (1.1% in the placebo-controlled studies and 0.3% in the ipratropium-controlled studies), or ipratropium (0.6%).

In the six-month studies, pharyngitis and sinusitis were more common in women (7.7% and 7.7%) than in men (3.5% and 1.9%) [iss.pdf/p49].

Because very few patients in these studies were non-white, analyses for drug-race safety interactions were not informative.

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Drug-disease interactions

There was no evidence of a drug-disease severity interaction, based on categories of diseases severity (FEV₁ <35%, FEV₁ 35-49%, and FEV₁ ≥50% predicted) [iss.pdf/p43, 50]. There was no evidence of a drug-smoking status interaction, based on smoking status at entry into the trial [iss.pdf/p43, 50].

Drug-drug interactions

The clinical development program did not include specific drug-drug interaction studies. Subgroup analyses of adverse event data from the “pivotal” Phase 3 studies were performed for baseline users vs. non-users of theophylline, oral corticosteroids, and inhaled corticosteroids. While the incidence of COPD exacerbations was greater in steroid users compared with steroid non-users, the Applicant states that there was no evidence of interaction of tiotropium with oral steroids or inhaled steroids on reported adverse events. In the one-year placebo controlled studies, the incidence of dry mouth in the tiotropium group was greater in theophylline users than in non-users (20% vs. 15%) [iss.pdf/p175]. No such difference was seen in the placebo group. In the 1-year ipratropium-controlled studies, reports of dry mouth were equally distributed in those receiving tiotropium who were theophylline users and non-users. Finally, in the six-month studies, the pattern was reversed, with a lower incidence of dry mouth among tiotropium patients who were theophylline users vs. non-users (2.7% vs. 10%) [iss.pdf/p48].

6. Safety Findings from Other Clinical Studies

COPD Studies

COPD studies discussed in this section include the AM/PM dosing trial (205.123), the mucociliary clearance trial (205.116), the sleep trial (205.124), the dose-ranging trials (205.119, 205.120, and 205.108), a pharmacokinetic trial in the elderly (205.133), and a trial conducted with the Respimat device (205.127) [iss.pdf/p50].

There were three deaths among these studies. The causes of death were myocardial infarction (11 weeks after the last dose of tiotropium in the pharmacokinetic trial in the elderly), respiratory failure (in a placebo patient in the sleep study), and non-Hodgkin's lymphoma (108 days following the two-week study period of a dose-ranging trial [205.120]). Few SAEs were reported in these relatively short studies. Few adverse events led to discontinuation, and such events were generally less common in the tiotropium groups. In the six-week AM/PM dosing study, one patient receiving PM tiotropium developed cystitis, hematuria, and orchitis requiring hospitalization. Study drug was discontinued [iss.pdf/p206]. One patient in the Respimat study (205.127) who was receiving tiotropium 2.5mcg developed worsening of hematuria that was considered unexpected and related to the study drug [iss.pdf/p206-7]. Of note, male rats developed proteinaceous material in the urinary bladder in the majority of preclinical studies [4/18/02 submission, iss.pdf/p272]. This was associated with a mild inflammatory response and diffuse hyperplasia of the bladder transitional epithelium, and prostatitis.

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Asthma Studies

Among the four asthma studies (205.121, 205.201, 205.202, and 205.203), no deaths were reported and SAEs and AEs leading to discontinuation were few [iss.pdf/p208-9].

Healthy Volunteer Studies

The most common AEs in the single-dose studies were headache and taste perversion [iss.pdf/p209]. In the multiple-dose studies the most common AEs were dry mouth and taste perversion.

7. Adverse Events Related to the Pharmacologic Actions of the Drug

The Application included specific attention to adverse effects that might result from the anticholinergic effect of tiotropium. These include gastrointestinal effects (dry mouth, constipation, and dysphagia), cardiovascular effects (tachycardia), genitourinary effects (urinary retention, urinary tract infection), and ophthalmologic effects (glaucoma).

Dry Mouth

Dry mouth was consistently more common in tiotropium groups as compared with placebo and as compared with the active comparators, ipratropium and salmeterol. Dry mouth was more common in older patients and in women. The median onset of dry mouth, which was generally of mild or moderate intensity, was 15 to 35 days [iss.pdf/p211-3]. Severe dry mouth and discontinuation due to dry mouth were uncommon (three patients in each category in the one-year studies). In the one-year, placebo-controlled studies, tiotropium was also associated with increased frequency of certain adverse events that may be related to the drying effects of the drug. These include epistaxis (3.6% vs. 1.9%), pharyngitis (8.9% vs. 7.3%), sinusitis (11.3% vs. 9.4%), and moniliasis (3.6% vs. 2.4%) [iss.pdf/p212]. Among these, the frequency of pharyngitis, sinusitis, and moniliasis were greater in the tiotropium group (6.5%, 3.4%, and 2.8%, respectively) compared with the ipratropium group (2.8%, 2.2%, and 1.7%, respectively) in the one-year, ipratropium-controlled studies.

Constipation

In the one-year, placebo-controlled studies constipation was reported more frequently in the tiotropium group (3.5%) than in the placebo group (1.6%) [iss.pdf/p214]. One patient in the tiotropium group required hospitalization due to fecal impaction.

Dysphagia

Dysphagia was reported by three patients in the one-year studies. All three were in the tiotropium group [iss.pdf/p215]. Two of the patients underwent endoscopy as a result of the symptom.

Urinary Retention and Micturation Disorders

Urinary retention occurred in four patients (0.7%) receiving tiotropium in the one-year placebo-controlled studies [iss.pdf/216]. The four cases occurred between treatment days 18 and 174, in men between the ages of 69 and 77. All four required the placement of a Foley catheter and three were started on medication for BPH. Urinary retention also occurred in one patient receiving tiotropium in the six-month studies, but did not occur in any patients in the one-year,

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ipratropium-controlled studies [iss.pdf/p216]. In addition, there were four reports of micturation disorders in the tiotropium group (in men aged 64 to 81 years) and none in the placebo group of the one-year, placebo-controlled studies, and one case of micturation disorder in each of the two treatment arms of the one-year, ipratropium-controlled studies.

Urinary Tract Infection

In the one-year, placebo-controlled studies, the incidence of urinary tract infection was greater in the tiotropium group (6.5% vs. 4.0%) [iss.pdf/p217]. In the one-year, ipratropium-controlled studies the incidence of UTI was not different between the tiotropium and the ipratropium groups. However, the incidence of cystitis was greater in the tiotropium group in those studies (2.5% vs. 0.0%). In the six-month studies the incidence of UTI was 1.2% in the tiotropium and 0.5% in the placebo group.

Cardiovascular Effects

The incidence of death due to cardiac events was not different in the tiotropium and placebo groups in the one-year studies (0.5% vs. 0.3%). However, there were subtle indications that tiotropium may be associated with increased frequency of adverse cardiac effects, specifically in the category of “heart rate and rhythm disorders.” (Note: Cardiac AEs are divided into three categories: “general,” “heart rate and rhythm disorders,” and “myo-, endo-, pericardial and valve disorders.”) In the one-year, placebo-controlled studies the incidence of “heart rate and rhythm disorders” was greater in the tiotropium group (4.4%, 24 patients) than in the placebo group (2.2%, 8 patients) (see table below) [iss.pdf/p231]. It should be noted that in the one-year ipratropium-controlled studies the incidence of “heart rate and rhythm disorders” was greater in the ipratropium group (5.0%) than in the tiotropium group (3.9%). The incidence of serious “heart rate and rhythm disorders” in the one-year, placebo-controlled studies was 1.3% in the tiotropium group and 0.5% in the placebo group [iss.pdf/p232]. This included two SAEs of supraventricular tachycardia, both of which occurred in patients on tiotropium. In the one-year studies, there were four discontinuations due to heart rate and rhythm disorders, all in the tiotropium group [iss.pdf/p234]. In the one-year, placebo-controlled studies, there were two deaths due to heart rate and rhythm disorders, both in the tiotropium group [iss.pdf/p233]. Although there was no difference between groups for “Myo-, Endo-, Pericardial and Valve Disorders” AEs in the one-year, placebo-controlled studies, there was a slightly greater incidence of SAEs in this category (2.0% vs. 1.3%) [iss.pdf/p232].

Cardiac Adverse Events, by WHO System Organ Class (1-year studies)								[iss.pdf/p231]	
	1-year, placebo-controlled studies				1-year, ipratropium-controlled studies				
	Tiotropium		Placebo		Tiotropium		Ipratropium		
	N	(%)	N	(%)	N	(%)	N	(%)	
Total Treated	550	100	371	100	356	100	179	100	
Cardiovascular Disorders, General	5	0.9	5	1.3	3	0.8	3	1.7	
Cardiac Failure	5	0.9	4	1.1	1	0.3	1	0.6	
Cardiac Failure, Right	0	0	0	0	2	0.6	0	0	
Cardiomegaly	0	0	1	0.3	0	0	1	0.6	
Cor Pulmonale	0	0	1	0.3	0	0	0	0	
Heart Disorder	0	0	0	0	0	0	1	0.6	
Heart Valve Disorder	0	0	0	0	1	0.3	0	0	
Heart Rate and Rhythm Disorders	24	4.4	8	2.2	14	3.9	9	5.0	

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Cardiac Adverse Events, by WHO System Organ Class (1-year studies) [iss.pdf/p231]								
	1-year, placebo-controlled studies				1-year, ipratropium-controlled studies			
	Tiotropium		Placebo		Tiotropium		Ipratropium	
	N	(%)	N	(%)	N	(%)	N	(%)
Total Treated	550	100	371	100	356	100	179	100
Arrhythmia	4	0.7	1	0.3	0	0	1	0.6
AV Block	0	0	0	0	1	0.3	1	0.6
Bradycardia	1	0.2	1	0.3	0	0	0	0
Bundle Branch Block	0	0	0	0	1	0.3	0	0
Cardiac Arrest	1	0.2	0	0	0	0	0	0
Extrasystoles	2	0.4	0	0	0	0	0	0
Fibrillation Atrial	5	0.9	3	0.8	5	1.4	4	2.2
Palpitation	4	0.7	2	0.5	3	0.8	3	1.7
Sick Sinus Syndrome	1	0.2	0	0	0	0	0	0
Tachycardia	4	0.7	1	0.3	4	1.1	0	0
Tachycardia supraventricular	2	0.4	1	0.3	0	0	0	0
Myo-, Endo-, and Pericardial and Valve Dis	15	2.7	10	2.7	10	2.8	6	3.4
Angina Pectoris	4	0.7	2	0.5	6	1.7	4	2.2
Angina Pectoris Aggravated	2	0.4	0	0	1	0.3	1	0.6
Cardiomyopathy	1	0.2	0	0	0	0	0	0
Coronary Artery Disorder	4	0.7	4	1.1	0	0	0	0
Heart Murmur	0	0	2	0.5	0	0	0	0
Myocardial Infarction	3	0.5	2	0.5	3	0.8	1	0.6
Thrombosis Coronary	1	0.2	0	0	0	0	0	0

In the one-year, placebo-controlled studies ECGs were done at baseline and every 90 days for the duration of the study. *Unfortunately, the protocol did not specify the timing of the ECGs in relation to study drug and that information was not captured on the case report forms [Submission date 7/16/02, page 5].* Therefore, it cannot be assumed that the ECGs were obtained at or near the expected C_{max}. In these studies, there was no difference between groups in the incidence of ECG changes (1% vs. 1.8%). The Applicant states that there was no imbalance in regard to the type of ECG abnormalities noted. One patient in the one-year, ipratropium-controlled studies developed tachycardia 30 minutes after the first dose of tiotropium and discontinued the study.

In the six-month studies, ECGs were performed at baseline and at the completion of the study. The incidence of ECG changes was 1.7% in the tiotropium group and 0.8% in the placebo group. In the four-week, parallel-group, placebo-controlled, dose-ranging study (205.108) ECGs were performed at baseline and at one, three, and five hours after drug administration on Day 1 and Weeks 1, 2, and 4. No differences in the occurrence of ECG changes was noted between active and placebo groups [iss.pdf/p225]. Tachyarrhythmias were seen in three tiotropium patients (ventricular tachycardia in a patient receiving 4.5mcg, atrial fibrillation in a patient receiving 9mg, and sinus tachycardia in a patient receiving 18mcg) and in one patient in the placebo group (sinus tachycardia).

The ECG database is supported by timed ECGs (1, 3, and 5 hours post-dose) that were performed in the multiple-dose, dose-ranging study (205.108). In that placebo-controlled study, doses of 5.5mcg, 11.0mcg, 22.0mcg, and 44.0mcg were studied (33-35 patients per treatment

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group). In addition to a baseline pre-dose ECG, timed ECGs (and 2-minute rhythm strips) were obtained after 8, 15, and 29 days of treatment [U96-3068.pdf/p111-14]. The ECGs and rhythm strips were centrally read by a cardiologist. There were no differences seen between placebo and active treatment in regard to ECG changes. Borderline QT interval was reported as intermittent in one placebo patient and transient in one tiotropium patient (22.0mcg). Specific QT or QTc interval data was not submitted.

Only one study included 24-hour Holter monitoring. This was the six-week, AM/PM dosing trial (205.123), in which there were three, double-blind treatment groups (tiotropium 18mcg AM dosing, tiotropium 18mcg PM dosing, and placebo, using the Handihaler device) [U00-0121.pdf]. The study was performed in the UK and the Netherlands, during the period May, 1997 to July, 1998 [U00-0121.pdf/p20]. Exclusion criteria were similar to other clinical studies. Patients with a history of significant disease other than COPD and patients with a recent history of heart failure or any cardiac arrhythmia requiring drug therapy were excluded. A total of 121 patients entered the trial (43 in the tiotropium PM dosing group, 38 in the tiotropium AM dosing group, and 40 patients in the placebo group). The mean age was 65.8 years, and 62% of the population was male. In this study, Holter monitoring was performed on two occasions. The baseline, 24-hour Holter monitor was placed on Day 0, and continued until Day 1, approximately 2 hours *after* the first dose of study medication [U00-0121.pdf/p44]. The second 24-Holter monitor was placed at Visit 4, at the end of the 6-week treatment period. The protocol does not specify when the monitor was placed in relation to study drug administration [U00-0121.pdf/p45]. The analysis of the Holter tapes was performed by a central facility (Hertford Medical, The Netherlands) [U00-0121.pdf/p41]. Data on supraventricular and ventricular ectopy, heart rate, and heart rate variability were collected and assessed [U00-0121.pdf/p101].

Reviewer's Comment: Interpretation of the comparisons of "baseline" and on-treatment Holter results is complicated by the fact that the first dose of study drug was given during the recording of the "baseline" Holter. *On-treatment Holter monitor results were available for 35 tiotropium PM patients, 37 tiotropium AM patients, and 31 placebo patients* [U00-0121.pdf/p103]. No clear effect on the frequency of supraventricular or ventricular ectopy was observed. No episodes of atrial fibrillation or atrial flutter were observed, either at baseline or on treatment [U00-0121.pdf/p104]. One subject in the tiotropium PM group developed a four-fold increase in ventricular ectopy after medication [U00-0121.pdf/p104]. None of the treatment groups had a remarkable change in mean heart rate, minimum heart rate, or maximum heart rate. There were no episodes of AV block. The Applicant states that assessment of heart rate variability is a sensitive marker of anticholinergic effects on the heart. In general, an increase in variability is said to indicate an improvement in cardiac autonomic function. The Applicant states that tiotropium was associated with a minor decrease in heart rate variability [iss.pdf/p228].

Ocular Events

The clinical studies did not suggest a drug-associated increase in the occurrence of glaucoma. In the one-year, placebo-controlled studies, glaucoma was reported in two patients receiving tiotropium and one patient receiving placebo [iss.pdf/p238]. In the one-year, ipratropium-controlled studies one case of glaucoma was reported in a patient receiving tiotropium. In the six-month studies, glaucoma was reported in one patient in the tiotropium group, one patient in

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the salmeterol group, and two patients in the placebo group. In a study evaluating the safety following ocular administration of single increasing doses of a solution of tiotropium ranging from 0.02 to 0.40 mcg, tiotropium did not increase pupillometric pressure or affect pupillary diameter in healthy volunteers (Study 205.138).

D. Adequacy of Safety Testing

The safety assessments performed in the pivotal studies were generally satisfactory, with one exception. The cardiac safety database is limited and does not provide sufficient evidence of cardiac safety for this drug. There are several reasons to be concerned about possible cardiac effects of tiotropium. First, anticholinergic drugs, such as tiotropium, might be expected to have effects on cardiac rate and rhythm. Second, the drug is associated with detectable plasma concentrations, particularly with chronic use. Third, underlying cardiac disease is common in the proposed patient population. As with most clinical development programs, subjects with significant cardiac disease (e.g. myocardial infarction within 1 year, heart failure within three years, cardiac arrhythmia requiring drug therapy, and significant disease other than COPD), subjects with hypoxemia requiring daytime oxygen therapy, and subjects with a creatinine >2.0 mg/dL were excluded from participation in the Phase 3 clinical studies. Such patients, who will receive the drug if it is approved, may be at increased risk of adverse drug-related cardiac effects. Finally, because of the large volume of distribution and long elimination half-life, subjects who develop adverse drug effects will continue to be exposed for weeks after discontinuing the drug.

The cardiac safety database includes insufficient Holter monitor data. Holter monitors were performed in only one study (205.123). In that study, "baseline" Holters included a period of time on drug, complicating the interpretation of the comparison of baseline to on-treatment data. On-treatment Holters were only available for 37 patients treated with the proposed dose in the morning, 35 patients treated with the proposed dose in the evening, and 31 placebo patients. For comparison, the product label for Serevent Inhalation Aerosol (GlaxoSmithKline) indicates that Holter monitoring was performed on 284 COPD patients during five 24-hour periods

Although the ECG monitoring in the one-year, placebo-controlled studies was less than optimal because the on-treatment ECGs were not obtained at or near the expected C_{max} (and may have been obtained pre-dose), the ECG database is supported by the timed ECGs from the multiple-dose, dose-ranging study (205.108).

E. Four-Month Safety Update

The Four-Month Safety Update, dated April 18, 2002, was submitted electronically. *The references cited in this section of the Medical Officer Review refer to the April 18, 2002, submission.* The submission included an updated Integrated Summary of Safety including new safety data covering the period of December 14, 2000 to December 13, 2001, and Clinical Trial Reports for two studies (205.131 and 205.222). Study 205.131 is discussed briefly below. Study 205.222 was a study of the effect of concomitant cimetidine and ranitidine once daily on the single dose pharmacokinetics of tiotropium, performed in 18 subjects in Germany [iss.pdf/p93]. The updated ISS includes preliminary unblinded safety data from four studies [iss.pdf/p24]:

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- an exercise study with a treatment period of six-weeks (205.131) [iss.pdf/p28];
- a study evaluating changes in inspiratory capacity with a treatment period of four-weeks (205.218) [iss.pdf/p28];
- a study to evaluate the effect of a single dose of ipratropium after 19 days of tiotropium treatment in healthy volunteers aged 40-65 years(205.239) [iss.pdf/p30];
- and a placebo-only HandiHaler ease-of-use and learning retention study (205.220) [iss.pdf/p28].

However, the updated ISS safety database includes only 18 subjects not reported in the original ISS [iss.pdf/p109]. These are the 18 healthy volunteers who participated in the IV pharmacokinetic trial (single doses of 14.4 mcg). The preliminary safety data from the four unblinded studies listed above, are discussed separately [iss.pdf/p287-95]. Review of that discussion did not reveal any new potential safety concerns.

The submission also provides information on 4 previously unreported deaths, which occurred in Study 205.214, an ongoing study evaluating the effect of tiotropium on the severity and incidence of COPD exacerbations [iss.pdf/p277-9]. The causes of death were pulmonary embolism, monocytic leukemia, myocardial infarction, and intestinal obstruction (post-operative). The treatment assignment has not been unblinded.

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CLINICAL REVIEW

Dosing, Regimen, and Administration Issues

VIII. Dosing, Regimen, and Administration Issues

The proposed dose and dosing interval are acceptable. However, the data supporting the specific dose is certainly less than optimal. Most of the dose-ranging used a previous version of the device, the only exception being a single-dose study performed in Japan. All of the dose-ranging studies, including the multiple-dose dose-ranging study, used a previous formulation, which differed from the Phase 3 formulation in regard to the lactose component. In Phase 3, a _____ lactose was added to the formulation, altering the particle size. This change in particle size was demonstrated to result in a change in urinary excretion values [biosum.pdf/p26]. Many of the crossover dose-ranging studies employed insufficient washout periods, and one dose-ranging study was not blinded. Therefore, there is no firm support for the proposed dose (18mcg). Approval must be based on established efficacy and safety.

Another factor that complicates the interpretation of the various dose-ranging studies is that, drug doses and concentrations were expressed differently during different periods of product development. Doses and concentrations were expressed either in terms of the salt (tiotropium bromide monohydrate) or, later (starting with Phase 3 in COPD, Studies 205.117 [U99-3169], 205.133 [U00-3029], 205.134 [U00-1289], 205.127 [U00-0077], 205.139 [study ongoing], 205.201 [U98-3174]), in terms of the cation (tiotropium). The change from using the salt to using the cation required adjustments in the actual drug content per capsule (_____ to round up label claims to whole numbers [biosum.pdf/p30]). Also, the dry powder capsules used during Phase 1 and 2 (Study 205.108, Report #U96-3068) contained _____ more tiotropium bromide monohydrate as the label claim, "due to historical reasons" [biosum.pdf/p32]. A '20mcg' inhalation capsule thus actually contained _____ of tiotropium bromide monohydrate (or _____ tiotropium). This was done because the Applicant's previous experience with other inhalation capsules showed that only about _____ of the content of an inhalation capsule actually leaves the capsule and the device during inhalation. However, subsequent analysis of tiotropium inhalation capsules showed that this percentage was not applicable. Therefore, prior to Phase 3, the actual dose in the capsule, rather than the "delivered dose" was labeled. The dose was also increased from _____ to 18mcg "for the sake of simplicity." [biosum.pdf/p32]

Based on the dose-ranging studies, the Applicant concluded that the _____ dose approached the plateau of the dose-response relationship. The 35.2mcg dose may have demonstrated a modest increase in efficacy but this benefit was diminished by the risk of greater adverse events, particularly dry mouth [hpsum.pdf/p54]. Given the limitations of the data discussed above, this conclusion seems reasonable. The Phase 3 safety and efficacy data can be considered further support for the dose chosen. In Phase 3, efficacy was demonstrated with adequate safety. Should further clinical experience suggest dose-related safety issues that have not yet been recognized, a lower dose could be investigated. The proposed dosing interval is supported by the trough FEV₁ data from the Phase 3 studies, which demonstrate efficacy at the end of the dosing interval.

CLINICAL REVIEW

Use in Special Populations

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The Applicant analyzed the adverse event data for potential gender interaction [iss.pdf/p177]. In the one-year, placebo-controlled studies, males accounted for 67% and 63% of the patients in the tiotropium and placebo groups, respectively. The proportion of patients with AEs was generally similar between genders, with the exception of dry mouth, which occurred in 23% of the women and 13% of the men in the tiotropium group. In the placebo group, the percentages were 2.9% of the women and 2.6% of the men. The reported term "urinary retention" only occurred in men in the tiotropium group (1.1%). In the six-month studies, dry mouth was also more common in women (14%) than men (6.4%) [iss.pdf/p202]. In these 6-month studies pharyngitis and sinusitis were also more common in women (7.7% and 7.7%) than in men (3.5% and 1.9%) in the tiotropium group.

The Applicant also analyzed the efficacy data for potential gender interaction [ise.pdf/p386]. For these analyses, the data from the identical (or nearly identical trials) were combined. That is, the two one-year, placebo-controlled trials were analyzed together, the data from the two one-year, active-controlled trials were analyzed together, and the data from the two six-month studies were analyzed together.

In the one-year, placebo-controlled studies, the mean average and peak FEV₁ responses were slightly higher in men than in women [ise.pdf/p487-8]. For instance, at Day 344 the mean average FEV₁ response (placebo-subtracted) was 0.22L for men and 0.18L for women. On the same test day, the mean peak FEV₁ response (placebo-subtracted) was 0.23L for men and 0.18L for women. The table below summarizes the mean peak FEV₁ data from the one-year, placebo-controlled studies, by gender. A similar pattern of greater FEV₁ response (average and peak) in men was seen in the 6-month studies [ise.pdf/p493-4]. Some of the difference in response may be related to gender-related differences in lung volumes. This is supported by the observation in the 6-month studies that the FEV₁ responses were also slightly (although to a lesser extent) greater in men in the salmeterol group. However, the observation of a gender interaction in regard to the TDI focal score (discussed below) might support a real gender effect.

Mean FEV ₁ Peak Response (Liters) (Combined 1-year, placebo-controlled studies) [ise.pdf/p488]				
Test Day	Gender	Tiotropium	Placebo	Difference
1	Male	0.25	0.09	0.16
	Female	0.20	0.06	
8	Male	0.31	0.09	0.22
	Female	0.26	0.06	
50	Male	0.31	0.09	0.22
	Female	0.24	0.06	
92	Male	0.29	0.06	0.19
	Female	0.24	0.05	
176	Male	0.29	0.05	0.23
	Female	0.24	0.02	
260	Male	0.28	0.06	0.22
	Female	0.21	0.05	