CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-030

MEDICAL REVIEW(S)

Financial Disclosure Review

Form FDA 3455 ("Financial Interests and Arrangements of Clinical Investigators"), dated Feb. 13th 2006, was submitted and reviewed by this clinical reviewer. In accordance with 21 CFR Part 54.4, certification and disclosure requirements, forms of clinical investigator certification and financial disclosure were also provided by Schwarz BioSciences, Inc.

In this financial disclosure submission all investigators have provided financial disclosure information via questionnaires.

No clinical investigator participating in the submitted studies from any of the study sites had any disclosures in the categories of compensation potentially affected by the outcome of the covered study [21 CFR 54.4(a)(3)(i), 54.2 (a)], significant payments of other sorts from the sponsor of the covered study [21 CFR 54.4 (a)(3)(ii), 54.2(f)], proprietary interest in the tested product [21 CFR 54.4(a)(3)(iii), 54.2(c)], or significant equity interest in the sponsor of the covered study product [21 CFR 54.4(a)(3)(iv), 54.2(b)].

Reviewer's Comment:
There is no reason to suspect that the results of any of the studies submitted in support of this NDA were compromised due to financial arrangements between the sponsor and the clinical investigators.

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/s/

Suresh Kaul
10/20/2008 03:39:50 PM
MEDICAL OFFICER

NDA 22-030

Medical Officer's Review: Complete Response to Approvable

Date Submitted:	May 1, 2008
Date Received:	May 1, 2008
Date Review Completed:	October 9, 2008
PDUFA Goal Date:	November 3, 2008
Drug Product:	Toviaz (fesoterodine fumarate)
Dose and Formulation:	4mg and 8mg extended-release tablets
Sponsor:	Pfizer, Inc New York, N.Y.

Indication: Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and urinary frequency.

1. Regulatory History

NDA 22-030 was initially submitted by Schwarz Pharma and accepted for filing by the FDA on March 17, 2006 for the indication "treatment of symptoms that may occur in subjects with overactive bladder syndrome".

Under terms of an agreement with Pfizer, Inc., effective June 13, 2006, Schwarz Pharma transferred all of its rights in fesoterodine to Pfizer on an exclusive world wide basis.

In an Approvable letter to Schwarz Pharma on January 25, 2007, FDA requested: 1) that all manufacturing sites be made ready for pre-approval inspection, 2) that revised labeling be submitted, and 3) that another Safety Update be submitted, to include data from all non-clinical and clinical fesoterodine studies since the previous Safety Update.

This review focuses on the requested Safety Update submitted in the Complete Response to Approvable action. This final update includes new safety data, obtained since the cutoff date of the original NDA (October 14, 2005), from 3 long-term, open-label extension studies completed by Schwarz Pharma (Studies SP669, SP738, and SP739), and an ongoing 12-week, open-label study (A0021007), initiated by Pfizer, with data included as of January 1, 2008.

In addition, this Complete Response to Approvable includes two new Phase1 studies completed by Schwarz Pharma (Studies SP857 and SP877) and three new Phase1 studies conducted by Pfizer (Studies A0221004, A0221015 and A0221044) since the NDA. The Clinical Safety Update includes summarizes of safety from these 5 new Phase 1 studies.

1.0 2. Extent of Exposure to Fesoterodine

2.1 Overview of Extent of Exposure to Fesoterodine

The following table presents the study design, number of subjects who received fesoterodine, and duration of treatment in Study SP669, an extension of the Phase 2 study SP668, and one of the three open-label, long-term extension studies.

Table 1. Phase 2 open label studies of fesoterodine in subjects with overactive bladder (Schwarz)

Study number/study design/dosage	# Subjects receiving fesoterodine[a]	# Subjects receiving placebo[a]	Mean treatment duration on fesoterodine
SP669/Extension of SP668/ 2-phase multicenter, double-blind and open-label, long-term study to assess safety, tolerability, and efficacy in OAB/ fesoterodine SR 4mg, 8mg, and 12mg doses once daily in the double-blind phase; fesoterodine 4mg and 8mg doses once daily in the open-label phase	186 (125 new exposures[b])	0	639 days

OAB=overactive bladder, SR=sustained release

a. These subject exposures are based on the safety set (SS).

b. New exposures include 20 subjects who previously received placebo in the preceding double-blind study, and 105 "de novo" subjects who enrolled directly into SP669 without having participated in SP668.

Table 2 presents the study design, number of subjects who received fesoterodine, and durations of treatment in Studies SP738 and SP739, the two, open-label, long-term extension studies to the Schwarz Pharma Phase 3 studies SP583 and SP584, respectively.

Table 2. Phase 3 open label studies of fesoterodine in subjects with overactive bladder (Schwarz)

Study number/study design/dosage	# Subjects receiving fesoterodine[a]	# Subjects receiving placebo[a]	# Subjects receiving active control[a]	Mean treatment duration
SP738/Extension of SP583/ multicenter, open-label, long-term safety and efficacy in OAB/ fesoterodine 4mg and 8mg doses once daily	417 (218 new fesoterodine exposures)[b]	NA	NA	695 days
SP739/Extension of SP584/ multicenter, open-label, long-term safety and efficacy in OAB/ fesoterodine 4mg and 8mg doses once daily	473 (158 new fesoterodine exposures)[b]	NA	NA	584 days

OAB=overactive bladder, NA=not applicable, SR=sustained release

a. These subject exposures are based on the safety set (SS) for each study.

b. New exposures are defined as those who previously received placebo or tolterodine in the preceding double-blind studies.

The following table presents the study design, number of subjects receiving fesoterodine, and the duration of treatment in the Study A0021007, the new, open-label, Pfizer study in this report.

Table 3. Study A0221007: Open-Label Study (Pfizer)

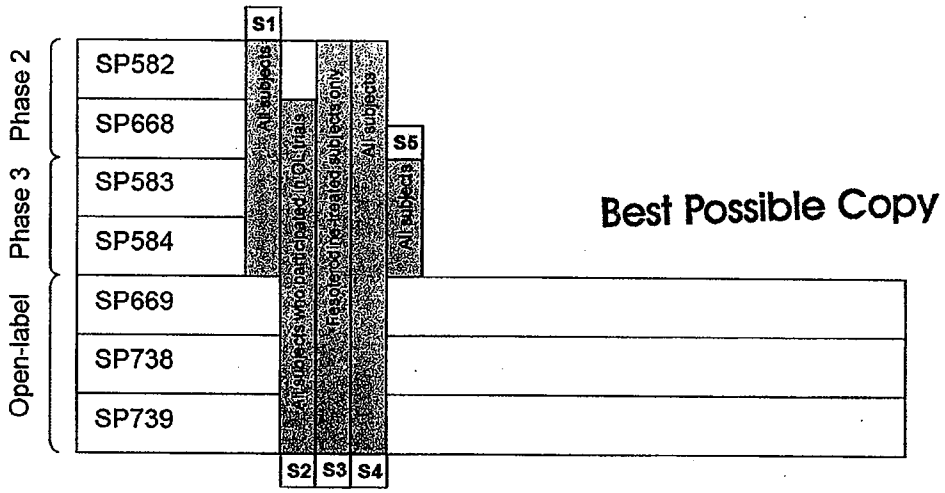
Study design/dosage	# Subjects receiving fesoterodine	# Subjects receiving placebo	# Subjects receiving active control	Median treatment duration
Twelve-week, multicenter, open-label study in OAB: fesoterodine 4mg and 8mg doses once daily	516	NA	NA	84 days

OAB=overactive bladder, NA=not applicable.

2.2 Integrated Safety Pools in the Final Safety Update

All safety pools are graphically illustrated in the following figure.

Figure 1. Description of safety pools (Schwarz Studies)



2.3 Overall Extent of Exposure (in Detail)

2.3.1 Schwarz Studies

Table 4 summarizes the overall exposure to fesoterodine in all Schwarz studies, including the NDA studies, their open-label extensions, and the 2 additional Phase 1 studies since the NDA.

Table 4. Schwarz Studies: Overall fesoterodine exposure

Population	Total Subjects n (%)[a]	Subject-years of exposure
Phase 1 (Pool P1)		
Intravenous formulation	28 (5)	NA
Immediate-release formulation	75 (13)	NA
Sustained-release formulations	525 (87)	NA
Additional Phase 1 (not pooled)		
Phase 2a (SP577)		
Immediate-release formulation	12 (100)	NA
Phase 2/3 (Pool S3) Sustained-release formulations		
≥0 months	2288 (100)	2112
≥6 months	857 (38)	1820
≥12 months	701 (31)	1711
≥18 months	615 (27)	1606
≥24 months	529 (23)	1457
≥36 months	105 (5)	367

Mean and median duration of exposure

Population	Mean / median (months)	
	Original NDA	FSU
Phase 2/3 (Pool S2, DB+OL)	13.5 / 13.4	23.1 / 26.3
Phase 2/3 (Pool S2, OL only)	11.7 / 11.6	21.3 / 25.4
Phase 2/3 (Pool S3)	7.6 / 3.2	12.0 / 3.2

DB=double-blind, FSU=Final Safety Update, NA=not applicable, NDA=New Drug Application, OL=open-label

a. Percentages based on number of subjects within each respective pool.

Overall, 2288 subjects received fesoterodine in the Phase 2 and 3 studies and another 525 received fesoterodine in the Phase 1 studies.

Reviewer's Comment: *Compared with the original NDA, the mean duration of exposure for Pool S2 increased by 10 months.*

2.3.2 Pfizer Studies: Conducted Since the NDA

In the three Pfizer Phase 1 studies (Studies A0221004, A0221015 and A0221044), 106 subjects were exposed to fesoterodine. The median duration of exposure for the 53 subjects administered fesoterodine 4mg was one day with a range of 1-5 days. The median duration of exposure for 53 subjects on fesoterodine 8mg was two days with a range of 2-5 days.

Study A0221007 was a 12-week study with a screening period of 2 weeks in which baseline OAB symptoms were assessed prior to baseline. Subjects not satisfied with their previous treatment with tolterodine or tolterodine ER and were bothered by OAB symptoms at baseline and met all other entry criteria were enrolled. All enrolled subjects were initially treated with fesoterodine 4mg QD for the first 4 weeks of treatment. At Week 4, based upon a discussion between the subjects and the investigators of efficacy and tolerability reported by the subjects, the investigator either increased the dose to 8mg QD for those who desired greater symptom improvement and reported good tolerability, or continued the subjects on 4mg QD dose, for the remaining 8 weeks of the study.

Five hundred and sixteen subjects with OAB received fesoterodine in Study A0221007. The median duration of exposure was 84 days and the range 3 – 109 days. Four hundred and thirty four subjects (434/486; 89.3%) received fesoterodine for > 60 days.

Table 5. **Pfizer Studies conducted since the NDA: Overall Fesoterodine Exposure**

Population	Total Subjects n (%)[a]	Subject-years of exposure
Phase 1 Studies	106[b]	NA
Study A0221007		
≤ 1 day	0	NA
2 – 7 days	9 (2)	NA
8 – 14 days	9 (2)	NA
15 – 28 days	7 (1)	NA
29 – 60 days	24 (5)	NA
61 – 90 days	442 (86)	NA
≥ 91 days	25 (5)	NA
Study A0221007- Median duration of exposure: 84 days; Mean duration of exposure: 79 days; Standard Deviation: 18 days Range: 3 – 108 days		

a. Percentages based on total number of subjects exposed.
b. Study A0221004: 16 subjects; Study A0221015: 16 subjects; Study A0221044: 36 subjects in a 3-way crossover study.

2.4 Exposure to Fesoterodine in the Long-Term Studies – Pool S2 (Schwarz NDA Open-Label Studies, All Participants). Pfizer Study A0221007 shown for comparison purposes.

Subjects treated in the open-label periods of the extension studies (Studies SP669, SP738, and SP739) are included in Pool S2. For the first analysis, data from prior Double-Blind Treatment Periods are included, while the second analysis included only data from open-label periods.

Safety data from the 12-week, open-label Study A0221007 conducted by Pfizer since the NDA are presented alongside to allow comparison.

2.4.1 Treatment duration, maximum daily dose, and daily dose of longest duration - Pool S2

Pool S2 (Schwarz NDA Open-Label Studies)

In Pool S2, mean treatment duration was 23 months (range: 1 day to 60 months) for the combined DB+OL periods, and 21 months (range: 1 day to 51 months) during OL only. The median maximum daily dose and median dose of longest duration was fesoterodine 8mg/day using both analysis approaches in Pool S2.

Study A0221007 (Pfizer)

The median treatment duration in this study was 84 days (range 3 – 108 days). Four hundred and forty two subjects were on fesoterodine for 61 – 90 days (442/516 subjects; 86%). The maximum daily dose used in this study was fesoterodine 8mg/day and dose of longest duration was fesoterodine 4mg/day.

2.4.2 Exposure by maximum daily dose - Pool S2

Pool S2 (Schwarz NDA Open-Label Studies)

In Pool S2 (DB+OL), most subjects (1040/1055: 99%) received a maximum daily fesoterodine dose of 8mg. A total of 522/1040 (50%) of these subjects were exposed to fesoterodine 8mg/day for more than 24 months, including 101 (10%) subjects exposed to the 8mg dose for more than 36 months.

During the OL only periods (Pool S2) a total of 512/1054 (49%) subjects were exposed to fesoterodine 8mg/day for more than 24 months, including 78 (7%) exposed to the 8mg dose for more than 36 months.

Study A0221007 (Pfizer)

A total of 258/516 (50%) subjects were exposed to fesoterodine 8mg. Two hundred forty four subjects (95%) received the 8mg/day for > 70 days.

2.4.3. Exposure by daily dose of longest duration - Pool S2

Pool S2 (Schwarz NDA Open-Label Studies)

The daily fesoterodine dose of longest duration for most subjects (848/1055: 80%) in Pool S2 (DB+OL) was 8mg/day. A fesoterodine dose of 4mg/day was the daily dose of longest duration for 204/1055 (19%) subjects, while fesoterodine 12mg/day was the daily dose of longest duration for 3/1055 (<1%) subjects.

Among subjects in Pool S2 (DB+OL) for whom 8mg/day was the daily dose of longest duration, 436/848 (51%) subjects were exposed to fesoterodine 8mg/day for more than 24 months, including 92 (11%) exposed to the 8mg/day dose for more than 36 months. When double-blind data are excluded, 421/894 (47%) subjects were exposed to fesoterodine 8mg/day for more than 24 months, including 68 (8%) exposed to the 8mg/day dose for more than 36 months.

The daily fesoterodine dose of longest duration for most subjects (894/1055: 85%) in Pool S2 (OL only) was 8mg/day, while fesoterodine 4mg/day was the daily dose of longest duration for 161/1055 (15%) subjects.

Study A0221007 (Pfizer)

The daily fesoterodine dose of longest duration for most subjects in Study A0221007 was 4mg/day (271/516: 53%), while fesoterodine 8mg/day was the daily dose of longest duration for 245/516 (47%) subjects.

For the subjects in whom 8mg/day was the daily dose of longest duration, 243/245 (99%) subjects were exposed to fesoterodine 8mg/day for > 70 days. For the subjects in whom 4mg/day

was the daily dose of longest duration, 222/271 (82%) subjects were exposed to fesoterodine 4mg/day for > 70 days.

2.4.4 Fesoterodine dose modifications during open-label treatment – Pool S2

Pool S2 (Schwarz NDA Open-Label Studies)
All subjects started on a fesoterodine dose of 8mg/day, but were allowed to switch to 4mg/day, and back to 8mg/day on an annual basis (except for SP669 where a decrease to 4mg/day and a subsequent dose increase back to 8mg/day was allowed only once during the study). The majority of subjects (825/1055: 78%) remained on the open-label starting dose of fesoterodine 8mg/day. A total of 178/1055 (17%) subjects reduced their dose to 4mg/day, and remained on this dose. Forty-three subjects (4%) re-escalated to fesoterodine 8mg/day.

Study A0221007 (Pfizer)

In this open-label study all enrolled subjects were initially treated with fesoterodine 4mg/day for the first 4 weeks of treatment. At Week 4, based upon a discussion between the subjects and the investigators of efficacy and tolerability reported by the subjects, the investigator either increased the dose to 8mg/day for those who desired greater symptom improvement and reported good tolerability, or continued the subjects on 4mg/day dose, for the remaining 8 weeks of the study.

Two hundred and fifty eight subjects (258/516: 50%) remained on the open-label starting dose of fesoterodine 4mg/day. A total of 255/516 (49%) subjects increased their dose to 8mg/day, and remained on this dose. One other subject who had titrated up to 8mg/day then titrated down to 4mg/day and subsequently titrated up to 8mg/day again and another subject who had titrated up to 8mg/day titrated down to 4mg/day. There was one subject who had received 8mg/day through-out the study.

2.5 Exposure to Fesoterodine in the Long-Term Studies – Pool S3 (All Phase 2/3 Schwarz Studies, Fesoterodine-Treated Subjects Only)

In Pool S3, median treatment duration was 23 months. Most subjects received fesoterodine 8mg/day.

2.5.1 Exposure by maximum daily dose – Pool S3

Among subjects treated with any dose of fesoterodine (Pool S3), 1759/2288 (77%) were exposed for up to 24 months. An additional 529/2288 (23%) subjects were exposed to fesoterodine for more than 24 months, including 105/2288 (5%) subjects who were exposed for more than 36 months.

The maximum daily dose of fesoterodine received by most subjects (1554/2288: 68%) in Pool S3 was 8mg. Fesoterodine 4mg/day was the maximum dose for 512/2288 (22%) subjects, while fesoterodine 12mg/day was the maximum daily dose for 222/2288 (10%) subjects.

2.5.2 Exposure by daily dose of longest duration – Pool S3

Among subjects treated with fesoterodine (Pool S3), the daily fesoterodine dose of longest duration for most subjects (1362/2288: 60%) was 8mg/day. Fesoterodine 4mg/day was the daily dose of longest duration for 715/2288 (31%) subjects, while fesoterodine 12mg/day was the daily dose of longest duration for 211/2288 (9%) subjects.

2.6 All Treated Subjects From Phase 2/3 Studies – Pool S4 (Schwarz Studies)

Fesoterodine exposure was greatest in the 8mg/day group at 1638 subject-years. This was followed by the fesoterodine 4mg/day group at 433 subject-years, and the fesoterodine 12mg/day group at 43 subject-years.

2.7 Summary of Exposure

Overall, 2288 subjects (Pool S3) received fesoterodine SR in Phase 2 or Phase 3 studies during the Schwarz development program for fesoterodine. A total of 529 subjects were exposed to fesoterodine for over 24 months, including 105 who were exposed for more than 36 months. Median treatment duration for fesoterodine-treated subjects (Pool S3) was 3.2 months, with most subjects receiving fesoterodine 8mg/day.

In the long-term pool, including data from the combined DB+OL periods (Pool S2), most subjects took fesoterodine 8mg/day for a mean duration of 23 months, ranging from a minimum of 1 day to a maximum of 60 months.

In Study A0221007 a total of 516 subjects received fesoterodine. Four hundred and forty two subjects received fesoterodine for between 61 – 90 days (442/516 subjects; 86%) and a further 25 subjects received the drug for ≥ 91 days. The median treatment duration was 84 days with half the subjects who initially received 4mg/day were subsequently exposed to 8mg/day (258/516) while the remaining half chose to continue with 4mg/day.

> ***Reviewer's Comment**: The extent of exposure to fesoterodine in clinical trials exceeds the ICH guidance criteria. There is safety data from >500 subjects and >100 subjects exposed for at least 2 years and at least 3 years, respectively.*

b(4)

3. Subject Disposition in the Studies Comprising the NDA and Final Safety Update

Side-by-side comparisons of subject disposition from the original NDA and this Final Safety Update are provided in the following table.

Table 6. Schwarz NDA Open Label Studies: Summary of subject disposition (Pool S2)

Parameter	Original NDA (OL only) N=1055 n (%)	FSU (OL only) N=1055 n (%)
Subjects treated	1055 (100)	1055 (100)
Subjects discontinuing treatment period	390 (37)	635 (60)
Reasons for discontinuation		
Protocol violation	5 (<1)	11 (1)
Lack of efficacy	97 (9)	141 (13)
Adverse event	117 (11)	150 (14)
Unsatisfactory compliance of subject	9 (<1)	22 (2)
Subject withdrew consent	99 (9)	165 (16)
Lost to follow-up	45 (4)	72 (7)
Other	18 (2)	75 (7)

FSU=Final Safety Update, NDA=New Drug Application, OL=open-label

In Pool S2 635/1055 60% subjects discontinued treatment prematurely. The most common reasons for discontinuation of open-label treatment in Pool S2, as recorded on the study termination page of the CRF, were withdrawal of consent (165/1055: 16%), adverse event (AE) (150/1055: 14%), and lack of efficacy (141/1055: 13%). Compared with the original NDA, the number of subjects in Pool S2 (OL only) who discontinued treatment prematurely because of withdrawal of consent increased by 66 (6%), the number who discontinued because of AEs increased by 33 (3%), and the number of subjects who discontinued because of lack of efficacy increased by 44 (4%) since the original NDA.

In comparison, in Study A0221007 a total of 53/516 subjects (10%) discontinued from the study prematurely. The most common reasons for discontinuing were adverse events and subject defaults. Discontinuations from the study were judged to be related to the study drug for 33 subjects (6%), and a majority of them were due to adverse events (29 subjects; 6%). The data are summarized in the table below.

Table 7. Study A0221007: Reasons for Discontinuation from Study

Total Number of Subjects: 486	
Discontinuations	**Number (%) of Subjects**
Related to Study Drug	
Adverse Event	29 (6)
Lack of Efficacy	4 (<1)
Not Related to Study Drug	
Adverse Event	7 (1)
Lost to Follow Up	2 (<1)
Other	4 (<1)
Subject defaulted	7 (1)

3.1 All Treated Subjects From Phase 2/3 studies – Pool S3 (Schwarz Studies)

Of the 2288 subjects included in Pool S3, 961 (42%) discontinued treatment prematurely.

Consistent with findings in Pool S2, the most common reasons for discontinuation were AE's (266/2288: 12%), withdrawal of consent (238/2288: 10%), and lack of efficacy (156/2288: 7%).

3.2 All Treated Subjects From Phase 2/3 studies – Pool S4 (Schwarz Studies)

Of the 2964 subjects included in Pool S4, 1098 (37%) discontinued treatment prematurely.

The most common reasons for discontinuation of treatment in Pool S4 were AE (305/2964; 10%), withdrawal of consent (269/2964; 9%), and lack of efficacy (165/2964; 6%).

In Pool S4, 3% to 8% of subjects in double-blind studies (Studies SP582, SP583, SP584, SP668, and SP669DB) discontinued due to an AE, compared with 10% to 24% of subjects in open-label studies (SP669, SP738, and SP739). The longer period of observation in the open-label studies probably contributes to the higher proportions of AE-related discontinuations.

> ***Reviewer's Comment:*** *The subject discontinuation rates and reasons for discontinuation are reasonable for this indication. Overall, the available data from all Phase 2 and Phase 3 studies allows for a complete overview of safety during fesoterodine exposure.*

3.3. Summary of Subject Disposition

3.3.1 Schwarz Studies

In the pool of subjects treated long-term (Pool S2), 635/1055 (60%) discontinued treatment prematurely, mostly due to withdrawal of consent (165/1055; 16%), AEs (150/1055; 14%), and lack of efficacy (141/1055; 13%). In the pool of all subjects (Pool S3), 961/2288 (42%) discontinued prematurely, the majority due to AEs (12%).

Disposition among all treated subjects (Pool S4) and reasons for discontinuation were also similar to those observed in Pool S3: 37% discontinued prematurely, 10% due to AEs.

3.3.2 Study A0221007 (Pfizer)

In Study A0221007, 53/516 (10%) subjects discontinued prematurely mostly due to AE's (36/516; 7%) and subjects defaulting (7/516; 1%).

> ***Reviewer's Comment:*** *The shorter duration of this study (12 weeks as opposed to long-term) is presumably the reason for fewer discontinuations compared to the NDA open-label studies.*

4. Demographic and Other Characteristics of Study Population

Schwarz Studies

Demographic tables were not rerun for the NDA studies conducted by Schwarz for the Final Safety Update as these data did not change.

Study A0221007 (Pfizer)

Demographic characteristics for Study A0221007 are presented in the following table. A majority of the subjects were white females in the age group 45 – 64 years (mean age of 59.4 years). The demography of subjects in this study are similar to the subjects enrolled in the studies in the NDA.

Table 8. Study A0221007: Demographic Characteristics

	Male Number (%) of Subjects N = 118	Female Number (%) of Subjects N = 398	Total Number (%) of Subjects N = 516
Age (years)			
< 18	0	0	0
18 – 44	6 (5.1)	70 (17.6)	76 (14.7)
45 – 64	49 (41.5)	176 (44.2)	225 (43.6)
≥ 65	63 (53.4)	152 (38.2)	215 (41.7)
Mean	64.0	58.3	59.6
SD	11.9	13.8	13.6
Range	19 - 83	19 - 90	19 – 90
Race			
White	92 (78.0)	303 (76.1)	395 (76.6)
Black	5 (4.2)	5 (1.3)	10 (1.9)
Asian	21 (17.8)	76 (19.1)	97 (18.8)
Other	0	14 (3.5)	14 (2.7)
Weight (kg)			
Number	116 (98.3)	397 (99.7)	513 (99.4)
Mean	84.0	73.4	75.8
SD	16.5	16.9	17.4
Range	44.0 – 140.6	41.0 – 158.7	41.0 – 158.7
Height (cm)			
Number	116 (98.3)	397 (99.7)	513 (99.4)
Mean	174.3	161.9	164.7
SD	8.2	7.1	9.0
Range	150.0 – 205.7	140.0 – 186.0	140.0 – 205.7

4.1 Eligibility Criteria for the OAB Program

4.1.1 NDA Studies (Schwarz)

Eligibility criteria were described in the Summary of Clinical Safety in the original NDA. There is no new information concerning eligibility criteria.

4.1.2 Study A0221007 (Pfizer open-label study)

The eligibility criteria for inclusion in this study were subjects ≥ 18 years of age who had been treated with tolterodine for their OAB symptoms and had reported dissatisfaction with it. Their dissatisfaction with tolterodine treatment was documented in a Treatment Satisfaction Question prior to inclusion. The severity of urinary symptoms was also documented prior to inclusion and subjects with a mean urinary frequency of ≥ 8 micturitions per 24 hours and mean number of urgency episodes ≥ 3 per 24 hours, as verified by a screening micturition diary, were considered eligible. The primary objective of the study was to evaluate the effect of fesoterodine on patient satisfaction and OAB symptom relief in this group of subjects.

4.1.3 Phase 1 Studies

Schwarz Phase 1 studies

Two Phase 1 studies have been completed since the original NDA by Schwarz: Study SP857, a randomized, double-blind, placebo-controlled, dose-escalation study to investigate safety and tolerability of fesoterodine in healthy Japanese males, and Study SP877, a randomized, open-label, crossover study to investigate dose proportionality of the 4mg and 8mg tablets.

Pfizer Phase 1 studies

An additional three Phase 1 studies have been completed by Pfizer since the NDA: Studies A0221004, A0221015, and A0221044. Study A0221004 was a double-blind, placebo-controlled, multiple dose, randomized study to evaluate the safety and pharmacokinetics of fesoterodine sustained release tablets in healthy male subjects. Study A0221015 was another double-blind, placebo-controlled, multiple dose, randomized study to evaluate the safety and pharmacokinetics of fesoterodine sustained release tablets in healthy male subjects. Study A0221044 was an open-label, randomized, single-dose, 3-way crossover study to determine bioequivalence of two newly developed 4 mg and 8 mg dose-normalized formulations E1 of fesoterodine sustained release tablets as well as to determine bioequivalence of 8 mg formulation E1 and 8 mg formulation F of fesoterodine sustained release tablets in healthy subjects.

> ***Reviewer's Comment:*** *For complete review of these Phase 1 studies, the reader is referred to the Clinical Pharmacologist's review.*

4.2 Summary of Demographics and Baseline Characteristics

As no new subjects were exposed to fesoterodine for this Safety Update in the NDA studies, there are no overall changes to the demographics and baseline characteristics. Concomitant medication use during long-term studies was similar to that observed in the original NDA. The demographic characteristics of the subjects in Study A0221007 were broadly comparable to the subjects enrolled in the NDA studies. Majority of the subjects were white females with a mean age of 59 years. This was similar to that seen in the NDA.

5.0 Adverse Events in the Safety Update

The following AE results represent the cumulative data until finalization for Pools S2 and S3... Results for Pool S1 and Pool S5 are not presented here as these data did not change since the original NDA. Data were analyzed in 2 ways for Pool S2. In one analysis, data from Double-Blind Treatment Periods and Open-Label Treatment Periods were combined (DB+OL). In the other analysis, only data from Open-Label Treatment Periods were used (OL only).

5.1 Common Adverse Events From Long-Term Studies – Pool S2 (Schwarz NDA Open-Label Studies). Study A0221007 (Pfizer) shown for comparison purposes.

Pool S2 (Schwarz NDA Open-Label Studies)

Table 9. Treatment-emergent adverse events reported by ≥2% of subjects (Pool S2: Schwarz NDA Open-Label Studies)

Preferred term	Original NDA (OL only) N=1055 n (%)	FSU (OL only) N=1055 n (%)
Dry mouth	296 (28)	322 (31)
Urinary tract infection	90 (9)	156 (15)
Constipation	57 (5)	80 (8)
Headache	48 (5)	52 (5)
Back pain	26 (3)	50 (5)
Nasopharyngitis	27 (3)	43 (4)
Hypertension	18 (2)	43 (4)
Diarrhea	33 (3)	41 (4)
Influenza	26 (3)	41 (4)
Upper respiratory tract infection	25 (2)	41 (4)
Gastroesophageal reflux disease	26 (3)	38 (4)
Bronchitis	17 (2)	38 (4)
Nausea	28 (3)	35 (3)
Cough	25 (2)	35 (3)
Sinusitis	20 (2)	34 (3)
Urinary retention	25 (2)	31 (3)
Dyspepsia	22 (2)	31 (3)
Cystitis	18 (2)	28 (3)
Dysuria	21 (2)	27 (3)
Dry eye	20 (2)	25 (2)
Rash	15 (1)	25 (2)
Dizziness	20 (2)	23 (2)
Abdominal pain	18 (2)	22 (2)
Vomiting	13 (1)	19 (2)
Edema peripheral	13 (1)	19 (2)
Dry throat	15 (1)	16 (2)

FSU=Final Safety Update, NDA=New Drug Application, OL=open-label

Study A0221007 (Pfizer)

There were 230 subjects who suffered an adverse event in Study A0221007.

Adverse events reported in at least 2% of subjects treated with fesoterodine in Study A0221007 are presented in the following table and compared with the incidences seen in the NDA open-label studies presented above.

Table 10. Study A0221007: Treatment-emergent adverse events reported by ≥2% of subjects

Preferred term	Study A0221007 N=516 n (%)	FSU (NDA OL only) N=1055 n (%)
Dry mouth	120 (23)	322 (31)
Constipation	25 (5)	80 (8)
Headache	20 (4)	52 (5)
Abdominal pain*	16 (3)	22 (2)
Diarrhoea	12 (2)	41 (4)

FSU=Final Safety Update, NDA=New Drug Application, OL=open-label. * = includes the terms abdominal pain, abdominal pain lower, abdominal pain upper and abdominal discomfort

The pattern of adverse events seen in Study A0221007 was similar to that seen in the NDA open-label studies. The most common AE's were dry mouth, constipation and headache.

5.2 Common AEs in Subjects Exposed to Fesoterodine – Pool S3 (Schwarz Studies)

The following table describes the AE's seen in ≥ 2 % of subjects in Pool S3 (fesoterodine-treated subjects only).

Table 11. Treatment-emergent adverse events reported by ≥2% of subjects (Pool S3)

Preferred term	Original NDA N=2288 n (%)	FSU N=2288 N (%)
Dry mouth	828 (36)	854 (37)
Urinary tract infection	148 (7)	209 (9)
Headache	194 (9)	198 (9)
Constipation	148 (7)	170 (7)
Nasopharyngitis	77 (3)	92 (4)
Nausea	79 (4)	87 (4)
Back pain	58 (3)	82 (4)
Diarrhea	73 (3)	81 (4)
Influenza	63 (3)	78 (3)
Dyspepsia	65 (3)	75 (3)
Upper respiratory tract infection	53 (2)	67 (3)
Cough	56 (2)	66 (3)
Dysuria	57 (3)	63 (3)
Dry eye	57 (3)	62 (3)
Hypertension	36 (2)	60 (3)
Dizziness	55 (2)	57 (3)
Dry throat	55 (2)	56 (2)
Sinusitis	39 (2)	52 (2)
Urinary retention	44 (2)	51 (2)
Bronchitis	30 (1)	50 (2)
Abdominal pain upper	44 (2)	47 (2)
Gastroesophageal reflux disease	35 (2)	47 (2)

FSU=Final Safety Update, NDA=New Drug Application

5.3 Adverse Events in Phase 1 Studies

Schwarz Phase 1 studies

Since the original NDA, two Phase 1 studies have been completed. In Study SP877, a study of single doses of fesoterodine 4mg or 8mg, the most frequent AE was headache. In Study SP857, subjects were exposed to single doses of fesoterodine 4, 8, or 16mg or placebo. In this study, dry mouth was the most commonly reported AE. There were no SAEs or AEs leading to discontinuation in either of these studies. With the exception of 1 event of headache of moderate intensity in Study SP877, all AEs reported in these 2 studies were mild in intensity.

Pfizer Phase 1 studies

Pfizer conducted three Phase 1 studies since the NDA. In Study A0221004, a study of fesoterodine 4mg and 8mg and placebo administered for five days, the most frequent adverse event was somnolence. In Study A0221015, also of fesoterodine 4mg and 8mg and placebo administered for five days, the most frequent adverse event was headache. Study A0221044 was a randomized, open-label, three-way crossover, single dose study in which the subjects received a single fesoterodine 4 mg Formulation E1 tablet (Treatment A), a single fesoterodine 8 mg Formulation E1 tablet (Treatment B) or a single fesoterodine 8 mg Formulation F tablet (Treatment C) at the start of each of three periods of the study. The most common AE in this study was headache.

There were no SAEs or AEs leading to discontinuation in any of these studies and all AEs reported in these three studies were mild or moderate in intensity.

5.4 Time to First Onset of an Adverse Event in Long-term Studies – Pool S2 (Schwarz NDA Open-Label Studies). Study A0221007 (Pfizer) shown for comparison purposes.

Pool S2 (Schwarz NDA Open-Label Studies)

The number of subjects reporting first onset of an AE from any system organ class during OL only treatment declined over time. A total of 667/1055 (63%) subjects reported first onset of any AE during the first 6 months of open-label treatment, 81/793 (10%) subjects reported first onset of any AE during months 7 to 12, 63/680 (9%) subjects reported first onset of an AE during months 13 to 24, and 19/512 (4%) subjects reported first onset of any AE during months 25 to 36. None of the 78 subjects with more than 36 months of fesoterodine treatment reported their first AE starting after 36 months.

Table 12. Adverse events by period of first onset reported by ≥5% of subjects overall (Pool S2 OL only)

Preferred term	First onset 1-6 months N=1055 n (%)	First onset 7-12 months N=793 n (%)	First onset 13-24 months N=680 n (%)	First onset 25-36 months N=512 n (%)	First onset >36 months N=78 n (%)
Dry mouth	298 (28)	9 (1)	13 (2)	2 (<1)	0
Urinary tract infection	61 (6)	28 (4)	47 (7)	17 (3)	3 (4)
Constipation	55 (5)	6 (<1)	13 (2)	5 (1)	1 (1)

NOTE: % refers to percentage of subjects among total (N).

First onset of dry mouth and constipation almost always occurred during the first 6 months of treatment. There was no clear trend for onset of first urinary tract infection (UTI).

Study A0221007 (Pfizer)

Study A0221007 was a 12-week open-label study. During this 12-week trial, the first onset of dry mouth and constipation occurred in 23% and 5% of all subjects respectively. This was consistent with the onset of these adverse events seen in the first six months of the long-term open-label studies presented in the NDA.

Pool S3 (Schwarz Studies) - All Fesoterodine-Treated Subjects in Phase 2/3 studies

Adverse events for subjects in Pool S3 were similar in type and distribution to those seen in Pool S1 in the original NDA, with dry mouth (37%), headache (9%), UTI (9%), and constipation (7%) reported by at least 5% of subjects.

As with Pool S2, the number of subjects reporting their first AE declined over time. A total of 1558/2288 (68%) subjects reported their first AE during the first 6 months of treatment, 55/857 (6%) subjects reported their first AE during months 7 to 12 of treatment, 45/701 (6%) subjects reported their first AE during months 13 to 24 of treatment, 14/529 (3%) subjects reported their first AE during months 25 to 36 of treatment, and no subjects reported their first AE after 36 months of treatment.

The onset patterns of the AEs listed above were similar to those seen during open-label treatment in Pool S2, with the majority of first onsets occurring during the first 6 months, followed by a sharp decline in first onsets thereafter. There was no clear trend for first onset of UTI.

5.5 Severity of Commonly Reported AEs

Subjects Treated in Open-Label Treatment Periods – Pool S2 (Schwarz NDA Open-Label Studies). Study A0221007 (Pfizer) shown for comparison purposes.

Pool S2 (Schwarz NDA Open-Label Studies)

Most treatment-emergent AEs were mild or moderate in intensity for the pool of subjects treated during Open-Label Treatment Periods. Adverse events with a maximum intensity of severe were

reported for 20% of subjects during OL-only treatment, representing a 6% increase over the percentage of severe AEs reported during the original NDA. Most of these severe AEs reflect the reporting of severe dry mouth and the increase from the original NDA is likely due to the longer observation period. Severe dry mouth, reported by 4% of subjects during OL-only treatment, and severe constipation, reported by 2% of subjects during OL-only treatment, were the only severe AEs reported by ≥ 1% of subjects in Pool S2.

Study A0221007 (Pfizer)

Most treatment-emergent adverse events were mild in severity in this study. Adverse events with a maximum intensity of severe were reported in 28 subjects (5%). The only severe events which were reported in > 1 subject in Study A0221007 were dry mouth (6 subjects; 1%, subjects), abdominal pain (3 subjects; <1%), and constipation (2 subjects; <1%). The only severe adverse event reported by ≥ 1% of all subjects was dry mouth.

Pool S3 (Schwarz Studies) - All Fesoterodine-Treated Subjects in Phase 2/3 studies

In Pool S3, most AEs were mild or moderate in intensity. Adverse events with a maximum intensity of severe were reported by 15% of subjects overall. As in the original NDA, severe dry mouth, reported by 4% of subjects, was the only severe AE that occurred in ≥1% of subjects in Pool S3.

5.6 Deaths

Schwarz NDA Studies

In all Schwarz studied combined, there were reports of 6 deaths, as shown in the table below.

Table 13. Subjects who had adverse events with fatal outcomes

Study number/ subject number	Dose and duration of study medication at onset of AE	Preferred term/ reported term	Causality (per investigator)
SP738/11047	Fesoterodine 8mg/day for 827 days	Cerebral infarction/right middle cerebral artery infarct	Not related
SP739/13686	Fesoterodine 8mg/day for 949 days	Death/Death	Not assessable (as per reporter)
SP738/11035	NA[a]	Hemorrhage intracranial/left parieto-occipital hemorrhage (intracranial haemorrhage)	Unlikely
SP669/12221	NA[b]	Pancreatic carcinoma/ pancreatic cancer	Not related
SP738/11255	NA[b]	Acute myeloid leukemia/ AML=acute myeloid leukemia	Unlikely
SP739/14862	NA[b]	Pancreatic carcinoma/ pancreatic carcinoma (metastatic)	Unlikely

AE=adverse event, NA=not applicable

a. Event occurred during the Safety Follow-Up Period.

b. Event occurred after the Safety Follow-Up Period (ie, AE was non-treatment-emergent).

Subject 11047, an 80-year-old male who had been taking fesoterodine 8mg/day during open-label treatment in Study SP738, died as the result of a cerebral infarction. The subject had taken tolterodine 4mg/day during the preceding Study SP583; his total fesoterodine exposure at the time of his death was 829 days. The investigator considered this fatal SAE to be not related to study medication.

Subject 13686, a 74-year-old Caucasian female with hypertension, hypercholesterolemia, hypothyroidism, gonarthritis, gastroesophageal reflux disease, and breast disorder had been taking fesoterodine 8mg/day during open-label treatment in Study SP739, died on Day 949. Concomitant medications included meloxicam, potassium chloride, levothyroxine, hydrochlorothiazide/triamterene, and metoprolol. Prior to open-label treatment, the subject had taken fesoterodine 4mg/day in Study SP584, for a combined double-blind plus open-label fesoterodine exposure of 949 days. Last contact with patient was on Day 896 and she reported no problems. The death was reported in an obituary in the local press, with no causality. Despite several attempts to reach family members in order to receive further information, the investigator was unsuccessful. The relationship to trial medication was reported as not assessable.

Subject 11035, an 84-year-old female who had been taking fesoterodine 8mg/day during open-label treatment in Study SP738, died as the result of an intracranial hemorrhage 6 days after discontinuation of fesoterodine; the onset of the event was 2 days after discontinuation of fesoterodine. Prior to open-label treatment, the subject had taken fesoterodine 8mg/day during Study SP583, for a combined double-blind plus open-label fesoterodine exposure of 573 days. The investigator considered this fatal SAE to be unlikely related to study medication.

Subject 12221, a 72-year-old female who had been taking fesoterodine 8mg/day during open-label treatment in Study SP669, died as the result of pancreatic cancer 99 days after discontinuation of fesoterodine; the onset of the event was 47 days after discontinuation of fesoterodine. Prior to open-label treatment, the subject had taken fesoterodine 8mg/day during Study SP668, for a combined double-blind plus open-label fesoterodine exposure of 1463 days. The investigator considered this fatal SAE to be not related to study medication.

Subject 11255, a 77-year-old male who had been taking fesoterodine 8mg/day during open-label treatment in Study SP738, died as the result of acute myeloid leukemia 114 days after discontinuation of fesoterodine; the onset of the event was 59 days after discontinuation of fesoterodine. Prior to open-label treatment, the subject had taken fesoterodine 8mg/day during Study SP583, for a combined double-blind plus open-label fesoterodine exposure of 560 days. The investigator considered this fatal SAE to be unlikely related to study medication.

Subject 14862, an 82-year-old male who had been taking fesoterodine 8mg/day during open-label treatment in Study SP739, died as the result of pancreatic carcinoma 147 days after discontinuation of fesoterodine; the onset of the event was 105 days after discontinuation of fesoterodine. Prior to open-label treatment, the subject had taken fesoterodine 4mg/day during Study SP584, for a combined double-blind plus open-label fesoterodine exposure of 456 days. The investigator considered this fatal SAE to be unlikely related to study medication.

Study A0221007 (Pfizer)

There were no deaths reported in this study.

5.7 Other Serious Adverse Events

5.7.1 Subjects Treated in Open-Label Treatment Periods – Pool S2 (Schwarz NDA Open-Label Studies). Study A0021007 (Pfizer) shown for comparison purposes.

Pool S2 (Schwarz NDA Open-Label Studies)

Serious treatment-emergent AEs reported by more than 2 subjects (all <1%) in Pool S2 during OL-only treatment for either the original NDA or this Final Safety Update are provided in the following table.

Table 14. Serious treatment-emergent adverse events reported by >2 subjects during OL only treatment (Pool S2)

Preferred term	Original NDA (OL only) N=1055 n	FSU (OL only) N=1055 n
Arthritis	4	6
Stress urinary incontinence	2	6
Myocardial infarction	4	5
Bronchitis	3	4
Breast cancer	3	4
Angina pectoris	2	4
Diverticulitis	2	4
Osteoarthritis	2	4
Cholecystectomy	3	3
Knee arthroplasty	3	3
Constipation	2	3
Hiatus hernia	2	3
Irritable bowel syndrome	2	3
Pneumonia	2	3
Intervertebral disc protrusion	2	3
Urinary retention	1	3
Hysterectomy	0	3

FSU=Final Safety Update, NDA=New Drug Application, OL=open-label, n=subjects

Note: This table is sorted in descending order by the FSU column.

Serious AEs were reported by 148/1055 (14%) subjects in Pool S2 during open-label treatment with fesoterodine. In the original NDA, 92/1055 (9%) subjects in Pool S2 reported SAEs during open-label fesoterodine treatment.

Compared with the original NDA, the number of subjects in Pool S2 (OL only) with stress urinary incontinence that was an SAE increased by 4 and the number of subjects with hysterectomy increased by 3. The events of arthritis, angina pectoris, diverticulitis, osteoarthritis, and urinary retention that were SAEs increased by 2 subjects each since the original NDA. The number of subjects with myocardial infarction, bronchitis, breast cancer, constipation, hiatus hernia, irritable bowel syndrome, pneumonia, or intervertebral disc protrusion reported as SAEs increased by 1 subject each.

Study A0221007 (Pfizer)

Serious adverse events were reported by 9/516 subjects (2%) in this study. None of the events occurred in more than one subject.

Pool S3 (All Fesoterodine-Treated Subjects in Phase 2/3 Schwarz Studies)

Serious treatment-emergent AEs reported by more than 2 subjects (all <1%) in Pool S3 for either the original NDA or this Final Safety Update are provided in the following table.

Serious AEs were reported by 213/2288 (9%) subjects in Pool S3, representing an additional 55 subjects (2%) reporting SAEs since the original NDA.

In Pool S3, 28/2288 (1%) subjects had SAEs considered by the investigator to be at least possibly treatment related. Most related SAEs occurred in 1 subject only, with the exception of urinary retention, which was considered at least possibly related to fesoterodine treatment in 3 of 3 cases, angina pectoris which was considered at least possibly related to fesoterodine treatment in 2 of 7 cases, diverticulitis, which was considered at least possibly related to fesoterodine treatment in 2 of 4 cases, and constipation, irritable bowel syndrome, and electrocardiogram QT corrected interval prolonged, each of which was considered at least possibly related to fesoterodine treatment in 2 of 3 cases.

Table 15. Serious treatment-emergent adverse events reported by >2 subjects (Pool S3)

Preferred term	Original NDA (Feso [DB+OL]) N=2288 n	FSU (Feso [DB+OL]) N=2288 n
Myocardial infarction	7	8
Angina pectoris	5	7
Arthritis	4	6
Stress urinary incontinence	2	6
Chest pain	5	5
Bronchitis	4	5
Pneumonia	4	5
Knee arthroplasty	4	4
Intervertebral disc protrusion	3	4
Breast cancer	3	4
Diverticulitis	2	4
Osteoarthritis	2	4
Appendicitis	3	3
Electrocardiogram QT corrected interval prolonged	3	3
Cholecystectomy	3	3
Constipation	2	3
Hiatus hernia	2	3
Irritable bowel syndrome	2	3
Urinary retention	1	3
Hysterectomy	0	3
Abdominal pain[a]	3	2

DB=double-blind, FSU=Final Safety Update, Feso=fesoterodine, NDA=New Drug Application, OL=open-label, n=subjects

Note: This table is sorted in descending order by the FSU column.

a. At the time of the original NDA, serious "abdominal pain" had been reported for 3 subjects in Pool S3. The seriousness of the event in 1 of these subjects was subsequently revised and categorized as nonserious.

Reviewer's Comment: Narratives for selected serious adverse events are presented in a separate "Narratives" section that follows below.

5.8 Adverse Events Leading to Subject Discontinuation

5.8.1 Serious adverse events leading to subject discontinuation - Long-term safety data – Pool S2 (Schwarz NDA Open-Label Studies). Study A0221007 (Pfizer) shown for comparison purposes.

Pool S2 (Schwarz NDA Open-Label Studies)

Serious AEs led to the discontinuation of 29/1055 (3%) subjects during OL only treatment. Urinary retention in 3 subjects discontinuing study medication, was the only SAE that led to discontinuation in more than 1 subject during OL only treatment.

Study A0221007 (Pfizer)

Serious adverse events led to discontinuation from the study in two subjects (<1%) in this study. The two serious adverse events causing the discontinuations were asthenia/lower extremity motor weakness and acute pyelonephritis.

5.8.2 Serious adverse events leading to subject discontinuation - All fesoterodine-treated subjects in Phase 2/3 studies – Pool S3 (Schwarz Studies)

In the pool of subjects exposed to fesoterodine, SAEs led to the discontinuation of 58/2288 (3%) subjects. Serious AEs that led to discontinuation in more than 1 subject included angina pectoris, myocardial infarction, electrocardiogram QT corrected interval prolonged, and urinary retention in 3 subjects each, and chest pain that led to early discontinuation of 2 subjects.

5.8.3 All adverse events leading to subject discontinuation - Long-term safety data – Pool S2 (Schwarz NDA Open-Label Studies). Study A0221007 (Pfizer) shown for comparison purposes.

Pool S2 (Schwarz NDA Open-Label Studies)

Treatment-emergent AEs led to discontinuation of fesoterodine in 138/1055 (13%) subjects during long-term treatment, and were typical of those seen during treatment with antimuscarinics. These included (in more than 2 subjects during open-label treatment) dry mouth in 19 (2%) subjects, urinary retention in 12 (1%) subjects, constipation in 10 (<1%) subjects, residual urine volume and dry eye in 5 (<1%) subjects each, electrocardiogram QT corrected interval prolonged in 4 (<1%) subjects, and cough, dry throat, alopecia, and dry skin in 3 (<1%) subjects each. This AE dropout profile is similar to that shown in the original NDA with the addition of electrocardiogram QT corrected interval prolonged and alopecia for this update.

5.8.4 All adverse events leading to subject discontinuation - fesoterodine-treated subjects in Phase 2/3 studies – Pool S3 (Schwarz Studies)

In the pool of subjects exposed to fesoterodine, AEs led to the discontinuation of 250/2288 (11%) subjects, and were often those associated with antimuscarinic treatment. This was an increase of 27 subjects since the original NDA. Adverse events leading to discontinuation of treatment in more than 3 subjects in Pool S3 are presented the following table.

Table 16. Treatment-emergent adverse events leading to discontinuation of treatment by >3 subjects (Pool S3)

Preferred term	Original NDA (Feso [DB+OL]) N=2288 n (%)	FSU (Feso [DB+OL]) N=2288 n (%)
Dry mouth	36 (2)	40 (2)
Urinary retention	21 (<1)	23 (1)
Constipation	11 (<1)	13 (<1)
Headache	9 (<1)	9 (<1)
Dry eye	9 (<1)	9 (<1)
Dry throat	8 (<1)	8 (<1)
ECG QT corrected interval prolonged	6 (<1)	8 (<1)
Residual urine volume[a]	8 (<1)	7 (<1)
Dyspepsia	5 (<1)	5 (<1)
Dizziness	5 (<1)	5 (<1)
Nausea	4 (<1)	5 (<1)
Abdominal pain lower	4 (<1)	4 (<1)
Vomiting	4 (<1)	4 (<1)
Vision blurred	4 (<1)	4 (<1)
Abdominal pain	3 (<1)	4 (<1)
Chest pain	3 (<1)	4 (<1)

DB=double-blind, ECG=electrocardiogram, Feso=fesoterodine, FSU=Final Safety Update, NDA=New Drug Application, OL=open-label

a. In the original NDA, 8 subjects had events of "residual urine volume" reported; one of these events was subsequently revised by the investigator and no longer considered an adverse event for the subject.

Reviewer's Comment: *The adverse events leading to discontinuation in these studies was consistent with the known characteristics of fesoterodine, and similar to that seen in the original NDA and the 120-day Safety Update. Narratives for selected adverse events leading to subject discontinuation are presented in a separate "Narratives" section that follows below. Cases of QT prolongation leading to subject discontinuation are reviewed individually in the Narratives section. These individual QT cases were ultimately determined to be minimal changes in the corrected QT interval without a clear relationship to fesoterodine.*

5.9 Dose reduction

Pool S2 (Schwarz NDA Open-Label Studies)

Overall 131/1055 (12%) subjects had their dose reduced from 8mg/day to 4mg/day during open-label treatment due to a treatment-emergent AE. Dry mouth in 93/1055 (9%) subjects was the AE most often leading to dose reduction during OL only treatment. This

was followed by constipation which led to dose reduction in 9 (<1%) subjects, dry eye and dysuria in 7 (<1%) subjects each, headache in 6 (<1%) subjects, urinary hesitation and dry skin in 4 (<1%) subjects each, and residual urine volume in 3 (<1%) subjects.

Study A0221007 (Pfizer)

Overall 7/516 subjects (1%) had their dose reduced or treatment temporarily discontinued due to treatment-emergent adverse events in this open-label study. The only adverse event which led to either dose reduction or temporary discontinuation in more than one patient was abdominal pain. Abdominal pain led to dose reduction/temporary discontinuation of the drug in three subjects (<1%).

5.10 Summary of adverse events

Schwarz NDA Studies

Dry mouth was the AE most often reported during open-label treatment (31%), followed by urinary tract infection (15%), constipation (8%), and headache (5%) in all subjects in Phase 2 and Phase 3 studies treated with fesoterodine (Pool S3) and in those seen in the primary safety pool (Pool S1) in the original NDA. Since the original NDA, the mean and median exposure to fesoterodine of subjects in Pool S2 (OL only) increased by 10 months and 14 months, respectively.

First onset of AEs was during the first 6 months of fesoterodine treatment for 63% of subjects, during months 7 to 12 for 10% of subjects, during months 13 to 24 for 9% of subjects, and during months 25 to 36 for 4% of subjects; no subjects reported a first onset AE after 36 months of treatment.

Most treatment-emergent AEs were mild or moderate in intensity for the pool of subjects treated during Open-Label Treatment Periods, with severe AEs reported by 20% of subjects during open-label treatment. Severe dry mouth (4%) and severe constipation (2%) were the only AEs reported as severe by ≥1% of subjects in Pool S2.

A total of 8 subjects died during the fesoterodine development program, including a placebo-treated subject who died several months after completing the study. Details of 5 of these cases were provided in the original NDA. Among the 3 subjects who died after the clinical cutoff for the original NDA, 1 subject treated with fesoterodine 8mg/day died of a cerebral infarction that was considered by the investigator to be unrelated to treatment with study medication and 1 subject treated with fesoterodine 8mg/day died of an unspecified cause, with the relationship to study medication reported as not assessable. The remaining subject died of an intracranial hemorrhage that began 2 days after fesoterodine was discontinued; the investigator considered the event to be unlikely related to study medication.

During long-term open-label treatment, SAEs occurred in 14% of subjects. Serious AEs reported by more than 2 subjects (all <1%) during open-label treatment were arthritis and stress

urinary incontinence in 6 subjects, myocardial infarction in 5 subjects, bronchitis, breast cancer, angina pectoris, diverticulitis, and osteoarthritis in 4 subjects, and cholecystectomy, knee arthroplasty, constipation, hiatus hernia, irritable bowel syndrome, pneumonia, intervertebral disc protrusion, urinary retention, and hysterectomy in 3 subjects.

Adverse events led to discontinuation of fesoterodine in 13% of subjects during long-term treatment. This percentage increased only slightly (from 11%) from the original NDA despite the longer observation period. Adverse events leading to discontinuation were typical of those seen during treatment with antimuscarinics, and included (in more than 2 subjects during open-label treatment) dry mouth in 19 (2%) subjects, urinary retention in 12 (1%) subjects, constipation in 10 (<1%) subjects, residual urine volume and dry eye in 5 (<1%) subjects each, electrocardiogram QT corrected interval prolonged in 4 (<1%) subjects, and cough, dry throat, alopecia, and dry skin in 3 (<1%) subjects each. Serious AEs led to the discontinuation of 29/1055 (3%) subjects during open-label treatment. Urinary retention, the reason for 3 subjects discontinuing study medication, was the only SAE that led to discontinuation in more than 1 subject during open-label treatment. With long-term fesoterodine treatment, the profile of common AEs, defined as those AEs occurring in at least 2% of subjects treated with any dose of fesoterodine, was similar to that seen and to those seen in the primary safety pool (Pool S1) in the original NDA. Since the original NDA, the mean and median exposure to fesoterodine of subjects in Pool S2 (OL only) increased by 10 months and 14 months, respectively.

Study A0221007 (Pfizer)

Dry mouth was the adverse event most often reported during this open-label study (23%), followed by constipation (5%), headache (4%) and abdominal pain (3%). The profile of common adverse events, defined as those adverse events occurring in at least 2% of subjects treated with any dose of fesoterodine, was similar to that seen in the NDA open-label studies although with a lower incidence.

Most treatment-emergent AEs were mild or moderate in intensity in this open-label study, with severe AEs reported by 5% of subjects. Severe dry mouth (1%) was the only AE reported as severe by $\geq$ 1% of subjects in study.

There were no deaths during the study. During this open-label study, SAEs occurred in nine subjects (2%). None of the SAEs were reported by more than one subject. Adverse events led to discontinuation of fesoterodine in 7% of subjects during this study. This percentage is less than that seen in the NDA open-label studies (14%). AEs leading to discontinuation were typical of those seen during treatment with antimuscarinics, and included (in more than 2 subjects) dry mouth in three (<1%) subjects, events pertaining to urinary retention, constipation and abdominal pain in two (<1%) subjects each. Serious adverse events led to the discontinuation of two (<1%) subjects during the study, the serious adverse events were lower extremity motor weakness and acute pyelonephritis.

There were no relevant differences in the incidence or profile of adverse events reported in this open-label study compared to the longer-term NDA open-label studies. Safety data from Study A0221007 have not identified any new safety concerns.

5.11 Narratives for subjects with serious adverse events and subjects who discontinued due to adverse events

5.11.1 Narratives for subjects with serious adverse events

Schwarz Studies

Short narratives and a table providing information on 5 subjects who died were provided in the Sponsor's Summary of Clinical Safety. Narratives for those deaths were provided in a previous section of this review. Narratives for SAEs were included with the individual clinical trial reports and are shown by trial and subject in the following tables. Only nonfatal, treatment-emergent SAEs for fesoterodine-treated subjects are referenced in the tables that follow.

The first table displays information by subject number for previously submitted SAE narratives that have been updated with new information, and the second shows information for narratives of new SAEs that were reported after the clinical cutoff date of the 120-Day Safety Update (01 Feb 2006).

Previously submitted narratives that did not require updates were described in the Sponsor's Summary of Clinical Safety in the original NDA as well as in the 120-Day Safety Update.

Table 17. List of previously submitted SAE narratives, updated with new information

Table 31. Schwarz NDA Studies: Updates to previously submitted SAE Narratives

Subject number	Age/ gender	AE preferred term	Daily dose at onset (mg/day)	Intensity	Causality
Updated narratives for fesoterodine-treated subjects with nonfatal, treatment-emergent SAEs					
SP669/11058	67/M	Brain neoplasm	4mg	Severe	Not related
SP668/11237	54/F	Depression Suicidal ideation	-- --	Severe Severe	Not related Not related
SP668/12190	55/F	Breast cancer	8mg	Severe	Unlikely
SP669/12221	72/F	Diverticulitis See also Narratives for subjects who died	8mg	Severe	Not related
SP669/13000	60/F	Atrioventricular block second degree Prinzmetal angina See also Narratives for fesoterodine-treated subjects who dropped out due to ECG changes	8mg 8mg	Moderate Moderate	Possible Possible
SP669/13164	71/F	Herpes esophagitis Herpetic stomatitis Pneumonia Chronic obstructive airways disease	8mg 8mg 8mg 8mg	Moderate Moderate Moderate Moderate	Not related Not related Not related Not related
SP669/13182	77/M	Myocardial infarction Gastric cancer	8mg 8mg	Mild Severe	Unlikely Not related
SP669/13187	74/F	Intervertebral disc protrusion (updated diagnosis: was reported as cerebrovascular accident in original application)	--	Mild	Not related
SP669/13426	65/F	Malignant melanoma Brain neoplasm malignant	8mg --	Severe Severe	Not related Not related
SP669/13581	76/F	Bronchitis Urinary tract infection pseudomonal Pelvic fracture Pulmonary embolism Pulmonary edema Pneumonia	4mg 4mg 4mg 4mg 4mg 4mg	Moderate Severe Moderate Severe Severe Moderate	Unlikely Not related Unlikely Not related Not related Not related
SP738/10340	69/M	Bronchitis Angina pectoris	8mg 8mg	Severe Severe	Not related Not related
SP739/13616	64/F	Bronchitis Breast cancer Constipation	8mg 8mg 8mg	Severe Moderate Severe	Not related Not related Unlikely
SP739/13800	85/F	Urinary retention Constipation	8mg 8mg	Severe Severe	Probable Probable
SP739/14379	72/F	Gait disturbance	4mg	Moderate	Not related
SP739/14718	82/M	Fall Contusion Hemorrhage urinary tract	8mg 8mg 8mg	Severe Severe Severe	Not related Not related Not related
SP739/14725	69/M	Adenocarcinoma	4mg	Moderate	Not related
SP739/14809	84/M	Knee arthroplasty	8mg	Severe	Not related
SP739/14861	58/F	Cholecystitis chronic Diabetic ketoacidosis Hernia repair Staphylococcal infection	8mg 8mg -- --	Severe Severe Severe Severe	Not related Not related Not related Not related
SP739/14894	66/F	Skin infection, Cellulitis	8mg	Severe	Not related

Table 17 (continued). List of previously submitted SAE narratives, updated with new information

Subject number	Age/ gender	AE preferred term	Daily dose at onset (mg/day)	Intensity	Causality
		Coronary artery bypass	8mg	Severe	Not related
SP738/11045	75/F	Chest pain	8mg	Moderate	Not related
SP738/11158	64/F	Urinary tract infection	8mg	Mild	Not related
		Diverticulitis	8mg	Severe	Possible
SP738/11211	60/M	Circulatory collapse	8mg	Moderate	Unlikely
		Dysarthria	8mg	Moderate	Unlikely
		Disorientation	8mg	Moderate	Unlikely
SP738/11237	69/F	Nerve root compression	4mg	Severe	Not related
		Goiter	4mg	Moderate	Possible
SP738/11259	80/F	Meniscus lesion	8mg	Moderate	Not related
		Rotator cuff syndrome	8mg	Moderate	Not related
		Diverticulitis	8mg	Severe	Not related
SP738/11262	57/F	Myocardial infarction	8mg	Moderate	Unlikely
SP738/11291	65/F	Liver abscess	8mg	Severe	Not related
		Urinary retention	8mg	Severe	Highly probable
SP738/11307	42/F	Hyperthyroidism	NA	Severe	Unlikely
SP738/11379	43/F	Appendicitis	8mg	Severe	Not related
		Menorrhagia	8mg	Severe	Not related
SP738/11421	74/M	Septoplasty	8mg	Moderate	Not related
		Surgery	8mg	Moderate	Not related
SP738/11438	74/F	Hiatus hernia	8mg	Severe	Not related
		Knee arthroplasty	8mg	Severe	Not related
		Wound infection	8mg	Severe	Not related
SP738/11440	76/M	Transient ischemic attack	8mg	Moderate	Unlikely
		Transient ischemic attack	8mg	Moderate	Unlikely
SP738/11443	73/F	Muscular weakness	8mg	Severe	Not related
		Nerve root compression	4mg	Severe	Unlikely
SP739/13589	42/F	Intervertebral disc protrusion	4mg	Severe	Unlikely

Table 18. List of new SAEs narratives, for cases reported after the clinical cutoff date of the 120-Day Safety Update

Table 32. Schwarz NDA Studies: New SAE Narratives

Subject number	Age/ gender	AE preferred term	Daily dose at onset (mg/day)	Intensity	Causality
New narratives for fesoterodine-treated subjects with nonfatal, treatment-emergent SAEs					
SP668/11024	59/F	Cellulitis	8mg	Severe	Not related
SP669/11051	64/F	Diverticulitis	--	Moderate	Not related
SP668/12099	60/F	Rotator cuff syndrome	8mg	Mild	Not related
SP668/12202	68/F	Pulmonary embolism Cholecystectomy	8mg 8mg	Severe Moderate	Not related Not related
SP669/13051	74/F	Non-Hodgkin lymphoma	8mg	Moderate	Not related
SP669/13283	68/F	Tibia fracture	8mg	Moderate	Not related
SP669/13356	25/F	Pancreatitis	--	Severe	Unlikely
SP738/10412	55/F	Vaginal prolapse	8mg	Moderate	Not related
SP738/10565	50/F	Carcinoembryonic antigen increased	8mg	Mild	Not related
SP738/10599	77/F	Hysterectomy	8mg	Moderate	Not related
SP738/10969	71/F	Osteoarthritis	8mg	Severe	Not related
SP738/10979	67/F	Nausea Headache	8mg 8mg	Severe Severe	Probable Probable
SP738/11078	60/F	Osteoarthritis	8mg	Severe	Not related
SP738/11082	51/F	Endometriosis	8mg	Severe	Not related
SP738/11086	38/F	Abortion spontaneous	NA	Severe	Possible
SP738/11146	54/F	Ventricular tachycardia	4mg	Moderate	Unlikely

Table 18 (continued). List of new SAEs narratives, for cases reported after the clinical cutoff date of the 120-Day Safety Update

Subject number	Age/ gender	AE preferred term	Daily dose at onset (mg/day)	Intensity	Causality
SP738/11160	57/F	Stress urinary incontinence	4mg	Moderate	Not related
SP738/11165	65/F	Arthroscopy	8mg	Severe	Not related
SP738/11167	56/F	Hiatus hernia	8mg	Severe	Not related
SP738/11225	49/F	Gastroesophageal reflux disease	8mg	Moderate	Not related
SP738/11231	69/F	Toe deformity Hip arthroplasty	8mg 8mg	Moderate Severe	Not related Not related
SP738/11241	65/F	Gouty tophus	8mg	Mild	Not related
SP738/11252	72/M	Angina pectoris	8mg	Severe	Unlikely
SP738/11311	70/F	Spigelian hernia	4mg	Severe	Unlikely
SP738/11336	40/F	Uterine leiomyoma	4mg	Moderate	Not related
SP738/11347	68/F	Gastrointestinal carcinoma Ileus Ileostomy closure	8mg 8mg 8mg	Mild Severe Severe	Unlikely Not related Not related
SP738/11366	60/F	Constipation	8mg	Mild	Probable
SP738/11411	39/F	Gastric banding	8mg	Moderate	Not related
SP738/11460	52/F	Bronchitis Ovarian cyst	8mg 8mg	Moderate Moderate	Unlikely Unlikely
SP738/11469	55/F	Stress urinary incontinence	8mg	Moderate	Not related
SP739/13306	55/M	Intervertebral disc compression	8mg	Moderate	Not related
SP739/13802	83/F	Incisional hernia Intestinal perforation	8mg 8mg	Severe Severe	Not related Unlikely
SP739/13869	26/F	Pregnancy	8mg	NA	Not related
SP739/13978	66/F	Electrocardiogram QT prolonged; Electrocardiogram T wave abnormal	8mg	Moderate	Possible
SP739/14056	67/F	Intracranial aneurysm	8mg	Severe	Not related
SP739/14225	52/F	Back pain	8mg	Severe	Not related
SP739/14306	56/F	Constipation, Amnesia	8mg	Moderate	Probably
SP739/14401	76/F	Gout	8mg	Severe	Not related
SP739/14450	70/F	Diverticulitis; Irritable Bowel Syndrome	8mg	Severe	Possible
SP739/14695	72/F	Pancreatitis	4mg	Severe	Not related
SP739/14754	57/F	White blood cell count increased	NA	Severe	Not related
SP739/14828	81/F	Sepsis	8mg	Severe	Not related
SP739/14862	82/M	Gastric ulcer	8mg	Mild	Not related

AE=adverse event, ECG=electrocardiogram, F=female, M=male, NA=not applicable, SAE=serious adverse event

Study A0221007 (Pfizer)

There were nine subjects (9/516 subjects; 2%) who experienced serious adverse events in this study. The table below provides a summary of all the serious adverse events in the study.

Table 19. List of SAE narratives for Pfizer Study A0221007

Table 33. Study A0221007: Serious Adverse Events

Subject number	Age. gender	AE MedDRA Preferred Term/Investigator Term	Fesoterodine daily dose	Outcome	Causality
10071013	73/F	Appendicitis/Acute Appendicitis	4mg	Recovered	Not related
10091005	54/F	Abdominal pain/Abdominal pain Renal mass/Renal mass Haemorrhoids/Hemorrhoids	8mg	Not recovered Not recovered Not recovered	Not related Not related Not related
10241009	62/M	Deafness unilateral/Hearing loss unilateral	8mg	Recovered	Not related
10251017	67/F	Hypertension/Hypertension	4mg	Recovered	Not related
10311011	72/F	Dyspnoea/Shortness of breath	8mg	Recovered	Not related
10801004	41/F	Asthenia/Asthenia	8mg	Recovered	Not related
10801020	72/F	Radius fracture/Radius fracture Joint sprain/Thumb sprain	8mg	Recovered Recovered	Not related Not related
1081101	63/F	Pyrexia/Fever	8mg	Recovered	Not related
10821012	62/F	Pyelonephritis acute/Acute pyelonephritis	4mg	Recovered	Not related

5.11.2 Narratives for subjects with SAE's of particular interest

Schwarz NDA studies

Subject 10979, a 67-year old female who had been taking fesoterodine 8mg/day during open-label treatment in SP738, developed severe nausea and headache requiring in-patient hospitalization with dose discontinuation. Subject recovered after 4 days without sequelae and dose was reduced to 4mg/day. The investigator considered the SAE to be "probably study-drug related". Two months later, subject experienced non-serious nausea and dropped out of study due to the AE. Total exposure to fesoterodine was 18 months.

Subject 11086, a 38-year old female who had been taking fesoterodine 8mg/day since November, 2004 (SP738), stopped contraception and fesoterodine on February 8, 2007 because of a planned pregnancy. Last menstrual period was January 13, 2007. A spontaneous abortion occurred on [redacted] The investigator considered this SAE to be "possibly related to study-drug". Total exposure to fesoterodine was 26 months. b(6)

Subject 13978, a 67-year old female who had been taking fesoterodine 8mg/day since July, 2004 (SP739), developed a prolonged QT detected on [redacted] The drug was withdrawn and subject was hospitalized. Subject did not recover from the prolonged QT and dropped out of study. Total exposure to fesoterodine was 31 months. The investigator considered this SAE to be "unlikely related to study-drug". b(6)

***Reviewer's Comments**: The spontaneous abortion occurred [redacted] months after stopping fesoterodine. The relationship to fesoterodine is unknown. All cases of QT prolongation*

were individually reviewed. In each case, the difference in corrected QT from baseline was very small and the relationship to fesoterodine was unclear. These are discussed in additional detail below.

5.11.3 Narratives for fesoterodine-treated subjects who discontinued because of an adverse event

Schwarz NDA Studies

In the original NDA, narratives for fesoterodine-treated subjects who discontinued treatment due to nonserious AEs for any of the following reasons were included in the respective clinical trial reports:

- ECG changes
- Constipation
- Tachycardia
- Increased residual urine
- Eye disorders
- Increase in transaminases

Subjects who discontinued for any of the reasons listed above are shown by trial and subject in the following tables. The first table displays information by subject number for previously submitted narratives that have been updated with new information. The second table shows information for narratives of subjects who discontinued the trial because of the AEs listed above after the clinical cutoff date of the 120-Day Safety Update.

Previously submitted narratives that did not require updates were described in the Sponsor's Summary of Clinical Safety in the original NDA as well as in the 120-Day Safety Update.

Table 20. List of previously submitted discontinuation narratives, updated with new information

Table 34. Schwarz NDA Studies: Updates to previously submitted narratives for AE Discontinuations

Subject number	Age/ gender	AE preferred term	Daily dose at onset (mg/day)	Intensity	Causality
Updated narratives for fesoterodine-treated subjects who dropped out due to ECG changes					
SP669/13000	60/F	Atrioventricular block second degree Prinzmetal angina See also Narratives for fesoterodine-treated subjects with nonfatal, treatment-emergent SAEs	8mg 8mg	Moderate Moderate	Possible Possible
Updated narratives for fesoterodine-treated subjects who dropped out due to constipation					
SP739/13800	85/F	See "Updated narratives for fesoterodine-treated subjects with nonfatal, treatment-emergent SAEs"			
Updated narratives for fesoterodine-treated subjects who dropped out as a result of tachycardia					
None					
Updated narratives for fesoterodine-treated subjects who dropped out due to increased residual urine					
SP738/11291	65/F	See "Updated narratives for fesoterodine-treated subjects with nonfatal, treatment-emergent SAEs"			
SP739/13800	85/F	See "Updated narratives for fesoterodine-treated subjects with nonfatal, treatment-emergent SAEs"			
Updated narratives for fesoterodine-treated subjects who dropped out due to eye disorders					
SP669/11238	57/F	Dry eye	8mg	Moderate	Highly probable
SP669/13185	60/F	Eye irritation	8mg	Mild	Not related
SP669/13186	55/F	Dry eye	8mg	Moderate	Highly probable
Updated narratives for fesoterodine-treated subjects who dropped out due increase in transaminases					
None					

Table 21. List of new discontinuation narratives, for cases reported after the clinical cutoff date of the 120-Day Safety Update

Table 35. Schwarz NDA Studies: New Narratives for AE Discontinuations

Subject number	Age/ gender	AE preferred term	Daily dose at onset (mg/day)	Intensity	Causality
Updated narratives for fesoterodine-treated subjects who dropped out due to ECG changes					
SP669/13000	60/F	Atrioventricular block second degree Prinzmetal angina See also Narratives for fesoterodine-treated subjects with nonfatal, treatment-emergent SAEs	8mg 8mg	Moderate Moderate	Possible Possible
Updated narratives for fesoterodine-treated subjects who dropped out due to constipation					
SP739/13800	85/F	See "Updated narratives for fesoterodine-treated subjects with nonfatal, treatment-emergent SAEs"			
Updated narratives for fesoterodine-treated subjects who dropped out as a result of tachycardia					
None					
Updated narratives for fesoterodine-treated subjects who dropped out due to increased residual urine					
SP738/11291	65/F	See "Updated narratives for fesoterodine-treated subjects with nonfatal, treatment-emergent SAEs"			
SP739/13800	85/F	See "Updated narratives for fesoterodine-treated subjects with nonfatal, treatment-emergent SAEs"			

Table 21 (continued). List of new discontinuation narratives, for cases reported after the clinical cutoff date of the 120-Day Safety Update

Subject number	Age/ gender	AE preferred term	Daily dose at onset (mg/day)	Intensity	Causality
Updated narratives for fesoterodine-treated subjects who dropped out due to eye disorders					
SP669/11238	57/F	Dry eye	8mg	Moderate	Highly probable
SP669/13185	60 F	Eye irritation	8mg	Mild	Not related
SP669 13186	55 F	Dry eye	8mg	Moderate	Highly probable
Updated narratives for fesoterodine-treated subjects who dropped out due increase in transaminases					
None					

AE=adverse event. ECG=electrocardiogram. F=female. M=male. SAE=serious adverse event

Study A0221007 (Pfizer)

A listing of the 36 subjects who discontinued the study due to an adverse event (36/516; 7%) is presented in the table below.

Table 22. List of discontinuations due to AEs for Pfizer Study A0221007

Table 36. Study A0221007: Discontinuations due to Adverse Events

Subject number	Age/ gender	AE MedDRA Preferred Term/Investigator Term	Intensity	Outcome	Causality	SAE
Gastrointestinal disorders						
10061009	53/F	Dry mouth/Dry mouth	Severe	Resolved	Related	No
10021002	78/M	Constipation/Constipation	Moderate	Resolved	Related	No
10071008	62/F	Abdominal pain upper/Stomach pain	Moderate	Resolved	Related	No
10421006	77/F	Diarrhoea/Diarrhea	Mild	Resolved	Related	No
10441002	66/F	Nausea/Nausea	Moderate	Resolved	Related	No
10441005	66/F	Gastritis/Gastritis	Moderate	Resolved	Not Related	No
10471017	43/F	Abdominal pain upper/Gastrodynia	Severe	Resolved	Related	No
10751005	36/F	Oesophagitis/Oesophagitis	Mild	Continuing	Related	No
10801002	76/F	Dry mouth/Dry mouth	Severe	Resolved	Related	No
10811013	69/F	Dry mouth/Dry mouth	Severe	Continuing	Related	No
10811014	44/F	Constipation/Constipation	Severe	Continuing	Related	No
10821026	66/F	Constipation/Constipation Headache/Headache	Mild Mild	Resolved Resolved	Related Related	No No
10401004	68/M	Dyspepsia/Heartburn	Mild	Resolved	Not Related	No
10811023	44/F	Abdominal distension/Abdominal distension Dysuria/urination pain	Severe Severe	Resolved Resolved	Related Related	No
Infections and infestations						
10561004	45/F	Cystitis/Cystitis	Severe	Resolved	Related	No
10821012	62/F	Pyelonephritis acute/Acute pyelonephritis	Severe	Resolved	Not Related	Yes

Table 22 (continued). List of discontinuations due to AEs for Pfizer Study A0221007

Injury, poisoning and procedural complications						
10801010	71/F	Back injury/Back sprain	Mild	Resolved	Not Related	No
Investigations						
10031002	66/M	Blood glucose increased/High blood sugar	Moderate	Resolved	Related	No
Metabolism and nutrition disorders						
10361005	73/F	Dehydration/Dehydration	Severe	Resolved	Related	No
10371003	51/F	Fluid retention/Fluid retention	Moderate	Resolved	Related	No
Musculoskeletal and connective tissue disorders						
10501004	41/F	Muscular weakness/Lower extremity motor weakness	Severe	Resolved	Not Related	Yes
Nervous system disorders						
10331003	37/F	Dysgeusia/Metal taste in mouth	Moderate	Resolved	Related	No
10351002	76/F	Balance disorder/Loss of balance	Moderate	Resolved	Related	No
		Oedema peripheral/edema of left leg	Mild	Resolved	Related	No
10821020	56/F	Headache/Headache	Mild	Resolved	Related	No
10841009	42/F	Dizziness/Dizziness	Moderate	Resolved	Related	No
		Headache/Headache	Moderate	Resolved	Related	No
Psychiatric disorders						
10021012	49/F	Euphoric mood/High feeling	Moderate	Resolved	Related	No
10821013	60/F	Insomnia/Insomnia	Severe	Resolved	Related	No
Renal and urinary disorders						
10361002	76/F	Urinary retention/Urinary retention	Moderate	Continuing	Related	No
10411002	75/F	Urinary retention/Acute urinary retention	Moderate	Resolved	Related	No
10801021	69/M	Dysuria/Voiding difficulty	Severe	Resolved	Related	No
10821024	44/M	Dysuria/Voiding difficulty	Mild	Resolved	Related	No
10821025	61/M	Dysuria/Voiding difficulty	Moderate	Resolved	Related	No
Reproductive system and breast disorders						
10551003	41/F	Genital haemorrhage/Transvaginal bleeding	Mild	Resolved	Not Related	No
Respiratory, thoracic and mediastinal disorders						
10091013	56/F	Cough/Dry cough	Mild	Resolved	Related	No
Skin and subcutaneous tissue disorders						
10751002	60/F	Hyperhidrosis/Hyperhidrosis	Moderate	Continuing	Related	No
Vascular disorders						
10551002	66/F	Hypertension/High blood pressure	Mild	Continuing	Not Related	No

Reviewer's Comments: *Review of the 10 cases reported as discontinuations due to QT prolongation adverse events indicated that only 5 of those subjects met the criterion for withdrawal (pre-defined as QTc Bazett > 500 ms or an individual increase in QTcB > 60 ms compared to baseline) and these were very modest increases (67, 68 and 70 ms over baseline in 3 cases and absolute corrected QT ranging from 509-527 ms in 4 cases). Two of the 3 cases were associated with an increased heart rate known to result in an overcorrection of QT using the Bazett formula. QT returned to normal within 2-6 weeks of discontinued drug. The prolongation of QT in a total of 7 other cases ranged from 23-54 ms. Only 1 case met both criteria for withdrawal; a 75 year old man taking 8 mg of drug for 118 days. Prolongation of QTcB interval was reported as 527 ms from 459 ms at baseline. This reviewer's conclusion essentially agrees with that of the reviewer of the original NDA submission that the reported QTc prolongations were mild in intensity, frequently related to co-morbidities and/or concomitant medications, and unlikely associated with fesoterodine.*

6. Clinical Laboratory Evaluations

6.1 Hematology, Chemistry and Urinalysis

Pool S2 (Schwarz NDA and Open-Label Studies)
There were no clinically relevant trends or changes in mean values for any hematology or urinalysis parameters from baseline to 6, 9, 12, 18, 24, or 36 months of treatment with open-label fesoterodine.

Laboratory abnormalities reported as AEs in ≥1% of subjects during open-label treatment included alanine aminotransferase increased and blood glucose increased in 2% of subjects each and blood creatine phosphokinase increased and gamma-glutamyltransferase increased in 1% of subjects each. No laboratory-related AE led to discontinuation in more than 1 subject during open-label treatment.

Overall in Pool S2, less than 1% of fesoterodine-treated subjects had an ALT elevation that was above 2.5 X ULN or a GGT elevation that was above 3 X ULN during open-label treatment. Elevation of AST above 2.5 X ULN and AP above 3 X ULN were each observed in 1 subject. There were no subjects in Pool S2 during the open-label periods with AST/ALT elevation above 2.5 X ULN + bilirubin above ULN.

6.2 Summary of clinical laboratory evaluations

Schwarz NDA Studies

There were no apparent trends in mean changes from baseline to the end of treatment or in shifts of clinical relevance over time in any hematology, clinical chemistry, or urinalysis parameters. Examination of individual clinically relevant laboratory abnormalities showed no clinically relevant pattern of laboratory abnormalities reported as AEs, AEs leading to withdrawal, or SAEs. While there were individual cases that exceeded the normal range for individual laboratory parameters, there were no trends in occurrences of markedly abnormal laboratory findings.

With respect to transaminases in particular, less than 1% of subjects had an abnormal hepatic laboratory parameter that was above the ULN cutpoint criteria (i.e., 2.5 X ULN for ALT and AST, 3 X ULN for GGT and AP) during open-label treatment. There were isolated cases of mild to moderate elevations in AST, ALT, and GGT, but no trends. No fesoterodine-treated subjects met the 10 X ULN cutpoint for any hepatic laboratory parameter. No fesoterodine-treated subject in Pool S2 had an AST/ALT elevation above 2.5 X ULN + bilirubin above ULN.

Overall, laboratory evaluations changed little during long-term open-label treatment and are similar to those reported in the original NDA. No new laboratory-related safety concerns have been identified.

7. Vital Signs, ECGs, Physical Findings, and Other Observations Related to Safety

7.1 Vital signs

Pool S2 (Schwarz NDA Open Label Studies)

Mean pulse rate increased (3.5bpm). This mean change from baseline is similar to that reported in the original NDA (3.4bpm) and the 120-Day Safety Update (3.6pbm). The long-term mean changes in vital signs, including pulse rate, from Pool S2 did not differ from those in Pool S1. There is no indication of increased effects on pulse rate with increased exposure. There were no changes in systolic or diastolic blood pressure.

The following table summarizes abnormal vital signs changes from Baseline for Pool S2. In keeping with the presentation provided for the NDA this table compares abnormal vital sign changes from baseline between the two treatment groups within Pool S2 (DB+OL and OL only).

Table 23. Abnormal vital signs changes from baseline (Schwarz studies Pool S2)

Vital sign/change criteria	(DB+OL) N=1055 n (%)	(OL only) N=1055 n (%)
Pulse rate		
≥15bpm increase	439 (42)	396 (38)
≥30bpm increase	55 (5)	52 (5)
≥15bpm decrease	134 (13)	121 (12)
≥30bpm decrease	6 (<1)	6 (<1)
Systolic blood pressure		
≥20mmHg increase	368 (35)	338 (32)
≥40mmHg increase	58 (6)	54 (5)
≥20mmHg decrease	365 (35)	339 (32)
≥40mmHg decrease	50 (5)	48 (5)
Diastolic blood pressure		
≥10mmHg increase	512 (49)	475 (45)
≥20mmHg increase	136 (13)	124 (12)
≥10mmHg decrease	591 (56)	560 (53)
≥20mmHg decrease	167 (16)	157 (15)

DB=double-blind, OL=open-label

Study A0221007 (Pfizer)

The mean change in systolic blood pressure from baseline to last observation for the subject population group was -0.6 mmHg and the mean change in diastolic blood pressure was -0.5 mmHg. The mean change in sitting heart rate from baseline to last observation was 0.8 bpm.

The table below summarizes abnormal vital signs changes from Baseline for Study A0221007 and compares it with changes seen in the Schwarz NDA open-label studies.

Table 24. Abnormal vital signs changes from baseline (Pfizer Study A0221007)

Vital sign/change criteria	Schwarz NDA OL Studies N=1055 n (%)	Study A0221007 N=482 n (%)
Pulse rate		
≥15bpm increase	396 (38)	61 (12)
≥30bpm increase	52 (5)	3 (<1)
≥15bpm decrease	121 (12)	33 (6)
≥30bpm decrease	6 (<1)	3 (<1)
Systolic blood pressure		
≥20mmHg increase	338 (32)	51 (10)
≥40mmHg increase	54 (5)	3 (<1)
≥20mmHg decrease	339 (32)	79 (15)
≥40mmHg decrease	48 (5)	6 (1)
Diastolic blood pressure		
≥10mmHg increase	475 (45)	145 (28)
≥20mmHg increase	124 (12)	20 (4)
≥10mmHg decrease	560 (53)	157 (31)
≥20mmHg decrease	157 (15)	28 (6)

DB=double-blind, OL=open-label

7.2 ECG Findings

No differences were observed in mean change from baseline in ECG results between the DB+OL and OL only periods. The following table summarizes change from baseline to end of treatment in ECG results for Pool S2.

Table 25. Changes from baseline to end of treatment (Schwarz studies Pool S2)

Parameter	DB+OL Mean (SD) N=1055	OL only Mean (SD) N=1055
Heart rate (bpm)	4.5 (9.98)	4.6 (9.98)
PR interval (ms)	-0.8 (15.14)	-0.8 (15.17)
QRS duration (ms)	-0.2 (8.34)	-0.3 (8.23)
QT interval (ms)	-7.9 (24.20)	-8.0 (24.21)
QTcF (ms)	0.3 (16.71)	0.3 (16.80)
QTcB (ms)	4.7 (19.52)	4.8 (19.62)

DB=double-blind, OL=open-label, SD=standard deviation

7.3 Residual Urine

In the pool of subjects treated in open-label periods, mean residual urine increased from 17mL at baseline to 27mL at 3 and at 6 months, 25mL at 12 months, 28mL at 18 months, and 27mL at 24 and at 36 months during open-label treatment. The mean residual urine at end of treatment using the last observation carried forward (LOCF) approach was 32mL, with a range from 0 to 480mL. The mean changes from baseline at months 3 through 36 (8 to 13mL) were comparable to that seen in the fesoterodine 8mg/day group (10mL) during double-blind treatment. The number of new subjects having a residual urine volume > 200mL are described in the following table.

Table 26. Subjects with residual urine > 200mL (Schwarz studies, Pool S2)

Subject number	Feso dose (mg/day)	Gender/age	Baseline[a] residual urine (mL)	Residual urine[b] >200mL/visit (mL)	Adverse Event[c] Yes/No
SP669					
13053	8	Male/73	74	232/Final visit	No
13430	8	Female/58	7	290/Final visit	No[d]
13575	4	Female/72	0	251/Final visit	No
SP738					
10835	8	Female/77	82	378/Final visit	Yes
10956	8	Female/48	0	410/Visit 6	Yes
11225	8	Female/47	45	282/Final visit	No
11248	8	Male/66	0	229/Visit 8	No
11388	8	Female/70	12	394/Final visit	Yes
SP739					
13273	8	Female/76	58	312/Visit 8	No
13593	8	Male/62	72	226/Final visit	No
13646	8	Female/46	57	232/Final visit	No
13665	8	Male/64	55	234/Final visit	No
13878	8	Female/62	0	342/Final visit	No
14051	8	Female/62	38	254/Final visit	No
14148	4	Female/70	76	240/Final visit	Yes
14251	8	Female/50	7	267/Visit 8	Yes
14470	8	Male/81	95	319/Final visit	No
14502	8	Female/75	34	462/Final Visit	Yes
14752	8	Female/47	49	282/Final visit	No

Feso=fesoterodine

7.4 Summary of vital signs, physical findings, and other observations related to safety

Schwarz NDA Studies

No clinically relevant changes from baseline were observed for vital sign parameters, ECG parameters, physical examination findings, or residual urine data during open-label treatment with fesoterodine.

Long-term treatment with fesoterodine does not appear to affect vital signs with the exception of a slight (4bpm) increase in mean pulse rate. This change was similar to the 2 to 3bpm increase seen in Pool S1 in the original NDA. Mean blood pressure remained stable from baseline to end of treatment. For ECG evaluations, mean heart rate increased by 5bpm. This increase was similar to that seen (3-6bpm) in the primary safety pool (Pool S1) in the original NDA. Increased heart rate is a known pharmacological effect of antimuscarinic drugs.

There was no indication of an increased incidence of QTc prolongation with increased exposure to fesoterodine over a 36-month period in Pool S2.

Two subjects had a maximum QTcF value that was at least 500ms during open-label treatment, and 3 subjects had maximum QTcF changes that were at least 60ms above baseline during open-label treatment. Six subjects had a maximum QTcB value that was at least 500ms during open-label treatment, and 10 subjects had maximum QTcB changes that were at least 60ms above baseline during open-label treatment.

In Pool S2, the proportions of subjects with prolonged PR intervals and prolonged QRS durations were similar at baseline and at end of treatment.

In summary, no clinically relevant mean changes from baseline were observed in heart rate, PR interval, QRS duration, QT interval, QTcF, or QTcB in Pool S2. There was no indication of an increased incidence of QT prolongation with long-term exposure to fesoterodine of up to 36 months during the OL only periods.

After an initial increase from baseline mean residual urine volume of 17mL to a mean of 27mL at months 3 and 6, mean residual urine volume leveled off with subsequent mean values of 25mL, 28mL, 27mL, and 27mL at Months 12, 18, 24, and 36, respectively. These increases in residual urine were similar to those seen in the primary safety pool (Pool S1) in the original NDA. A cumulative total of 43/1055 (4%) subjects treated in open-label periods had a residual urine volume >200mL, including 23 reported during the original NDA, and 20 reported in this safety update.

Study A02210007 (Pfizer)

No clinically relevant changes from baseline were observed for vital sign parameters in this study. There was a mean increase of 1bpm in heart rate from baseline to last observation, this change was less than the 4bpm increase seen in the NDA open-label studies. Mean blood pressure remained stable from baseline to end of treatment in this study.

8. Effect of patient age on treatment-emergent adverse events, laboratories and vital signs

8.1 Effect of patients age on adverse events (AESs)

Pool S2 (Schwarz NDA Open-Label Studies)

Constipation occurred more often in subjects ≥65 years (12%) than those <65 years (6%), and even more often in subjects ≥75 years (17%) than in those <75 years (7%). Dry mouth was reported by a similar proportion of subjects in subjects ≥ 65 years and < 65 years, but more frequently in subjects ≥75 years than in those <75 years.

Urinary tract infection was more common among subjects ≥75 years compared to those under 75 years of age (20% vs 14%, respectively), and this difference was larger than the comparison between subjects ≥65 years and those <65 years of age (17% vs 14%, respectively). Similarly, dizziness (at 8mg only) was a little more frequent among subjects ≥75 years compared to those under 75 years of age (5% vs 2%, respectively), which was slightly larger than the comparison between those ≥65 years and those <65 years of age (3% vs 2%, respectively). Increase in residual urine was also reported more frequently in subjects ≥75 years than in those <75 years. Headache was reported slightly more frequently in younger subjects (6% in those <65 years and 5% in those <75 years compared with 4% in those ≥65 years and 3% in those ≥75 years).

Study A0221007 (Pfizer)

Constipation occurred slightly more frequently in subjects ≥65 years (6%) than those <65 years (4%), and likewise slightly more often in subjects ≥75 years (6%) than in those <75 years (5%). Dry mouth was common in each age group occurring in 19% in the ≥75 years age group and 24% in the <75 years group. It was slightly more frequent in subjects < 65 years (26%) than subjects ≥65 years (20%).

Urinary tract infection was more common among subjects under 75 years (1.6%) compared to those ≥75 years of age in which group no urinary tract infections were reported, but this difference was reversed in the comparison between subjects ≥65 years and those <65 years of age (1.9% vs 1%, respectively). Dizziness was a little more frequent among subjects under 75 years (1.3%) compared to those ≥75 years of age in which group no adverse events of dizziness were reported. The same applied for adverse events of dizziness between those ≥65 years and those <65 years of age (0.9% vs 1.3%, respectively). Urinary retention was also reported more frequently in subjects ≥65 years (1.4%) than those <65 years in which group no urinary retentions were reported, and more frequently in subjects ≥75 years (4.3%) than in those <75 years in which group no urinary retentions were reported either. Headache was reported slightly more frequently in younger subjects (4.3% in those <65 years and 3.8% in those <75 years compared with 2.8% in those ≥65 years and 2.9% in those ≥75 years).

8.2 Effect of patient age on laboratory values

Time point values, change from baseline to end of treatment, maximum value during treatment, and minimum value during treatment were provided by age group for hematology, chemistry, and urinalyses parameters, and there were no clinically relevant trends or changes from baseline to end of treatment by age in both the Schwarz NDA or the Pfizer studies.

8.3 Effect of patient age on vital signs

Schwarz NDA Studies

Vital signs changes from baseline to end of treatment are shown by age group and summarized in the following table.

Table 27. Abnormal vital signs change from baseline to end of treatment (Schwarz Studies Pool S2)

Vital sign/change criteria	<65 years N=691 n (%)	≥65 years N=362 n (%)	<75 years N=944 n (%)	≥75 years N=109 n (%)
Pulse rate				
≥15bpm increase	93 (14)	40 (11)	123 (13)	10 (9)
≥30bpm increase	11 (2)	3 (<1)	14 (2)	0
≥15bpm decrease	23 (3)	10 (3)	32 (3)	1 (<1)
≥30bpm decrease	1 (<1)	0	1 (<1)	0
Systolic blood pressure				
≥20mmHg increase	75 (11)	42 (12)	99 (11)	18 (17)
≥40mmHg increase	5 (<1)	8 (2)	10 (1)	3 (3)
≥20mmHg decrease	65 (9)	55 (15)	102 (11)	18 (17)
≥40mmHg decrease	4 (<1)	11 (3)	12 (1)	3 (3)
Diastolic blood pressure				
≥10mmHg increase	134 (19)	81 (22)	195 (21)	20 (18)
≥20mmHg increase	28 (4)	16 (4)	39 (4)	5 (5)
≥10mmHg decrease	140 (20)	91 (25)	204 (22)	27 (25)
≥20mmHg decrease	23 (3)	17 (5)	33 (4)	7 (6)

Study A0221007 (Pfizer)

Vital signs changes from baseline to end of treatment by age group for Study A0221007 are summarized in the following table. No clinically relevant differences were observed between the age groups in change from baseline in vital signs.

Table 28. Study A0221007; Abnormal vital signs change from Baseline to end of treatment

Reviewer's Comment: *Analyses by Sponsor of treatment-emergent adverse events by age in Pool S1 of the Schwarz studies revealed that dry mouth, constipation, dyspepsia, increase in residual urine, dizziness (at 8mg only), and urinary tract infection were more commonly reported in subjects ≥ 75 years of age as compared to subjects <75 years. These differences are described in the Geriatric Use section of the package insert.*

Current review of the commonly reported TEAEs by age group in the original NDA and the Final Safety Update (FSU) indicated that for any system organ class in the age group ≥ 75 there were 123/208 AEs (59%) in the NDA vs 131/208 (64%) in the FSU.

9. Summary and Conclusions

This Safety Update presents new data from additional exposures in 3 long-term open-label extension studies (Studies SP669, SP738, and SP739) conducted by Schwarz. Data available from these studies at the time of filing were previously included in the NDA. Additional data in this Safety Update are those from an ongoing open-label study conducted by Pfizer, Study A0221007, from which no data had been included in the NDA.

The patient populations of these 4 open-label studies were similar to those in the NDA studies, however the exposure to study drug was much shorter in Study A0221007 (12 weeks) as compared to the 3 long-term open-label extensions (up to 36 months) that had been described in the original NDA.

The adverse event profile provided in this Safety Update is consistent with previously reported data in the original NDA and the 120-day Safety Update.

The most frequently reported adverse events were generally consistent across the studies and were similar to what was seen in the NDA. The majority of the common AEs reported in the NDA open-label studies (e.g., dry mouth, urinary tract infection, constipation and headache) were reported in much lower incidence in Pfizer Study A0221007, presumably due to the shorter duration of this open-label study. The incidence of SAEs and the rate of discontinuations due to AEs in the 3 long-term open label extension studies were similar to those seen in the original NDA. The incidences of SAEs and discontinuations due to AEs were again much lower in Study A0221007.

There were three treatment-emergent deaths and three non-treatment emergent deaths (i.e. deaths that occurred after the safety follow-up period for the studies) in the 3 long-term open label extension studies since the original NDA. Causality as assessed by the investigator was considered to be not related or unlikely to be related to fesoterodine for five deaths. In the other case, relationship to trial medication was reported as not assessable by the investigator.

There were no issues of concern with the laboratory test or ECG data in this Safety Update. Vital sign data reveal only the known modest increase in pulse rate associated with this antimuscurinic compound

Based on the new data that have become available since the previous submissions, the safety profile of fesoterodine remains unchanged compared to that described in the original NDA and the 120-day Safety Update. No new risks or safety issues have been identified by this review. The AEs of interest (dizziness, urinary tract infection, and urinary retention) are reported more frequently in geriatric patients aged 75 years and older.

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/s/

Harry Handelsman
10/7/2008 03:39:47 PM
MEDICAL OFFICER

Mark S. Hirsch
10/7/2008 10:53:02 PM
MEDICAL OFFICER
I concur.

NDA 22-030

Medical Officer's Filing Memorandum: Complete Response to Approvable

Date submitted:	May 1, 2008
Date received:	May 2, 2008
PDUFA date:	November 2, 2008
Date memo completed:	July 3, 2008
Sponsor:	Pfizer Global Pharmaceuticals
Drug Product:	Toviaz™ (fesoterodine fumurate)
Dosage strengths:	4mg and 8mg

Indication: For the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency.

1. Background

On January 25, 2007, the Office of Drug Evaluation 3 (ODE3) issued an "Approvable Action" for NDA 22-030 (fesoterodine fumarate for treatment of overactive bladder). The reasons for the Approvable action were as follows:

1. Pre-Approval Inspection (PAI) of the active pharmaceutical ingredient (API) manufacturing facility, Schwarz Pharma Ltd., located in Shannon, Ireland could not be conducted because the site had not been available for PAI during this review cycle. Satisfactory inspection of this API manufacturing facility was required before this application could be approved.

2. Labeling remained unresolved. Reference was made to revised labeling conveyed to the Sponsor on January 24, 2007, that was to serve as the basis for future discussions.

In addition to these two key Approvable issues, the January 25, 2007 letter stipulated that a ***Safety Update*** as described in 21 CFR 314.50(d)(5)(vi)(b) should be submitted with the Complete Response. The letter further stipulated that the safety update should include data from all non-clinical and clinical studies of fesoterodine regardless of indication, dosage form, or dose level and that the safety update should contain the following information in the following format:

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the re-tabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a re-tabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

On May 1, 2008, the Sponsor submitted a Complete Response to Approvable for NDA 22-030 which includes the required Safety Update.

The purpose of this memo is to provide an overview of the contents of the Safety Update as well as to convey any current Clinical review issues to the Sponsor.

2. Brief Overview of the Safety Update

This final Safety Update included results from three (3) long-term, open-label, extension studies conducted by Schwarz Pharma (studies SP 669, SP 738, and SP 739), as well as additional safety data from a new Pfizer study A0221007, which was of shorter duration (12 weeks).

According to the Sponsor, the patient population in these studies was similar to that in the original NDA, and the AE profile was also similar, with dry mouth, UTI, constipation, and headache being most commonly reported.

3. Brief Summary of Results From the Safety Update

3.1 Overall Adverse Events

Table 1 lists the treatment-emergent adverse events (TEAE's) reported by $\geq 2\%$ of subjects in the three, Schwarz, NDA open-label studies and compares their incidence rates between the original NDA and the Final Safety Update (FSU).

Table 1. TEAE's reported by ≥ 2% of subjects in the three, Schwarz, NDA open-label studies.

Preferred term	Original NDA N=2288 n (%)	FSU N=2288 N (%)
Dry mouth	828 (36)	854 (37)
Urinary tract infection	148 (7)	209 (9)
Headache	194 (9)	198 (9)
Constipation	148 (7)	170 (7)
Nasopharyngitis	77 (3)	92 (4)
Nausea	79 (4)	87 (4)
Back pain	58 (3)	82 (4)
Diarrhea	73 (3)	81 (4)
Influenza	63 (3)	78 (3)
Dyspepsia	65 (3)	75 (3)
Upper respiratory tract infection	53 (2)	67 (3)
Cough	56 (2)	66 (3)
Dysuria	57 (3)	63 (3)
Dry eye	57 (3)	62 (3)
Hypertension	36 (2)	60 (3)
Dizziness	55 (2)	57 (3)
Dry throat	55 (2)	56 (2)
Sinusitis	39 (2)	52 (2)
Urinary retention	44 (2)	51 (2)
Bronchitis	30 (1)	50 (2)
Abdominal pain upper	44 (2)	47 (2)
Gastroesophageal reflux disease	35 (2)	47 (2)

FSU=Final Safety Update, NDA=New Drug Application

Table 2 below lists the TEAE's reported by ≥ 2% of subjects in the more recent open-label Pfizer study, A0221007.

Table 2. TEAE's reported by ≥ 2% of subjects in the open-label Pfizer study, A0221007

Preferred term	Study A0221007 N=516 n (%)	FSU (NDA OL only) N=1055 n (%)
Dry mouth	120 (23)	322 (31)
Constipation	25 (5)	80 (8)
Headache	20 (4)	52 (5)
Abdominal pain*	16 (3)	22 (2)
Diarrhoea	12 (2)	41 (4)

FSU=Final Safety Update, NDA=New Drug Application, OL=open-label. * = includes the terms abdominal pain, abdominal pain lower, abdominal pain upper and abdominal discomfort

Reviewer's Comment: The overall adverse events in the Final Safety Update appear consistent with those in the original NDA and reflect the product's pharmacologic activity as an anticholinergic agent.

3.2 Serious Adverse Events (including Deaths) and Premature Discontinuations

3.2.1 Deaths

Six deaths (3 treatment-emergent and 3 non-treatment-emergent) were reported in the Schwarz Pharma, open-label, extension studies since the time of the original NDA.

Brief details of these six deaths are presented in Table 3, and complete narratives were submitted by Sponsor in the study reports.

Table 3. Brief details of the six deaths reported in the Schwarz, open-label, extension studies.

Study number/ subject number	Dose and duration of study medication at onset of AE	Preferred term/ reported term	Causality (per investigator)
SP738/11047	Fesoterodine 8mg/day for 827 days	Cerebral infarction/right middle cerebral artery infarct	Not related
SP739/13686	Fesoterodine 8mg/day for 949 days	Death/Death	Not assessable (as per reporter)
SP738/11035	NA[a]	Hemorrhage intracranial/left parieto-occipital hemorrhage (intracranial haemorrhage)	Unlikely
SP669/12221	NA[b]	Pancreatic carcinoma/ pancreatic cancer	Not related
SP738/11255	NA[b]	Acute myeloid leukemia/ AML=acute myeloid leukemia	Unlikely
SP739/14862	NA[b]	Pancreatic carcinoma/ pancreatic carcinoma (metastatic)	Unlikely

AE=adverse event, NA=not applicable

a. Event occurred during the Safety Follow-Up Period.

b. Event occurred after the Safety Follow-Up Period (ie, AE was non-treatment-emergent).

Data source: Appendix I FSU Table 27, FSU Listing 1

Reviewer's Comment: In none of the deaths was causality attributed to fesoterodine.

There were no deaths reported in Pfizer Study A0221007.

3.2.2 Serious Adverse Events

The following two tables provide a summary of new SAE's from the Schwarz Pharma open-label extension studies, reported after the cutoff date for the 120-day Safety Update, which was submitted with the original NDA (Feb. 2006) (Table 4); and all SAE's from Pfizer's new study (Table 5) .

Table 4. New SAE's reported after the cutoff date of the 120-day Safety Update which was submitted in the original NDA (Schwarz NDA Studies)

Subject number	Age/ gender	AE preferred term	Daily dose at onset (mg/day)	Intensity	Causality
New narratives for fesoterodine-treated subjects with nonfatal, treatment-emergent SAEs					
SP668/11024	59/F	Cellulitis	8mg	Severe	Not related
SP669/11051	64/F	Diverticulitis	--	Moderate	Not related
SP668/12099	60/F	Rotator cuff syndrome	8mg	Mild	Not related
SP668/12202	68/F	Pulmonary embolism Cholecystectomy	8mg 8mg	Severe Moderate	Not related Not related
SP669/13051	74/F	Non-Hodgkin lymphoma	8mg	Moderate	Not related
SP669/13283	68/F	Tibia fracture	8mg	Moderate	Not related
SP669/13356	25/F	Pancreatitis	--	Severe	Unlikely
SP738/10412	55/F	Vaginal prolapse	8mg	Moderate	Not related
SP738/10565	50/F	Carcinoembryonic antigen increased	8mg	Mild	Not related
SP738/10599	77/F	Hysterectomy	8mg	Moderate	Not related
SP738/10969	71/F	Osteoarthritis	8mg	Severe	Not related
SP738/10979	67/F	Nausea Headache	8mg 8mg	Severe Severe	Probable Probable
SP738/11078	60/F	Osteoarthritis	8mg	Severe	Not related
SP738/11082	51/F	Endometriosis	8mg	Severe	Not related
SP738/11086	38/F	Abortion spontaneous	NA	Severe	Possible
SP738/11146	54/F	Ventricular tachycardia	4mg	Moderate	Unlikely

Table 4 continued. New SAE's reported after the cutoff date of the 120-day Safety Update which was submitted in the original NDA (Schwarz NDA Studies)

Subject number	Age/ gender	AE preferred term	Daily dose at onset (mg/day)	Intensity	Causality
SP738/11160	57/F	Stress urinary incontinence	4mg	Moderate	Not related
SP738/11165	65/F	Arthroscopy	8mg	Severe	Not related
SP738/11167	56/F	Hiatus hernia	8mg	Severe	Not related
SP738/11225	49/F	Gastroesophageal reflux disease	8mg	Moderate	Not related
SP738/11231	69/F	Toe deformity Hip arthroplasty	8mg 8mg	Moderate Severe	Not related Not related
SP738/11241	65/F	Gouty tophus	8mg	Mild	Not related
SP738/11252	72/M	Angina pectoris	8mg	Severe	Unlikely
SP738/11311	70/F	Spigelian hernia	4mg	Severe	Unlikely
SP738/11336	40/F	Uterine leiomyoma	4mg	Moderate	Not related
SP738/11347	68/F	Gastrointestinal carcinoma Ileus Ileostomy closure	8mg 8mg 8mg	Mild Severe Severe	Unlikely Not related Not related
SP738/11366	60/F	Constipation	8mg	Mild	Probable
SP738/11411	39/F	Gastric banding	8mg	Moderate	Not related
SP738/11460	52/F	Bronchitis Ovarian cyst	8mg 8mg	Moderate Moderate	Unlikely Unlikely
SP738/11469	55/F	Stress urinary incontinence	8mg	Moderate	Not related
SP739/13306	55/M	Intervertebral disc compression	8mg	Moderate	Not related
SP739/13802	83/F	Incisional hernia Intestinal perforation	8mg 8mg	Severe Severe	Not related Unlikely
SP739/13869	26/F	Pregnancy	8mg	NA	Not related
SP739/13978	66/F	Electrocardiogram QT prolonged; Electrocardiogram T	8mg	Moderate	Possible

Table 5. SAE's from Pfizer Study A0221007

Subject number	Age/ gender	AE MedDRA Preferred Term/Investigator Term	Fesoterodine daily dose	Outcome	Causality
10071013	73/F	Appendicitis/Acute Appendicitis	4mg	Recovered	Not related
10091005	54/F	Abdominal pain/Abdominal pain Renal mass/Renal mass Haemorrhoids/Hemorrhoids	8mg	Not recovered Not recovered Not recovered	Not related Not related Not related
10241009	62/M	Deafness unilateral/Hearing loss unilateral	8mg	Recovered	Not related
10251017	67/F	Hypertension/Hypertension	4mg	Recovered	Not related
10311011	72/F	Dyspnoea/Shortness of breath	8mg	Recovered	Not related
10801004	41/F	Asthenia/Asthenia	8mg	Recovered	Not related
10801020	72/F	Radius fracture/Radius fracture Joint sprain/Thumb sprain	8mg	Recovered Recovered	Not related Not related
1081101	63/F	Pyrexia/Fever	8mg	Recovered	Not related
10821012	62/F	Pyelonephritis acute/Acute pyelonephritis	4mg	Recovered	Not related

Reviewer's Comment: The only serious adverse events cases judged by the investigator as being at least possibly related to fesoterodine (one patient each) included: constipation, QT prolonged, spontaneous abortion, and severe headache/nausea. These cases will be reviewed in greater detail. The Sponsor will be informed of this via regulatory letter.

3.2.3 Premature Discontinuations

The following two tables show brief information for those subjects who discontinued the trials because of AE's. Table 6 shows the cases from the Schwarz Pharma studies after the cutoff date of the 120-day Safety Update. Table 7 shows the cases from Pfizer's new study.

Table 6. New AE Discontinuations (Schwarz NDA Studies)

Subject number	Age/ gender	AE preferred term	Daily dose at onset (mg/day)	Intensity	Causality
Updated narratives for fesoterodine-treated subjects who dropped out due to ECG changes					
SP669/13000	60/F	Atrioventricular block second degree Prinzmetal angina See also Narratives for fesoterodine-treated subjects with nonfatal, treatment-emergent SAEs	8mg 8mg	Moderate Moderate	Possible Possible
Updated narratives for fesoterodine-treated subjects who dropped out due to constipation					
SP739/13800	85/F	See "Updated narratives for fesoterodine-treated subjects with nonfatal, treatment-emergent SAEs"			
Updated narratives for fesoterodine-treated subjects who dropped out as a result of tachycardia					
None					
Updated narratives for fesoterodine-treated subjects who dropped out due to increased residual urine					
SP738/11291	65/F	See "Updated narratives for fesoterodine-treated subjects with nonfatal, treatment-emergent SAEs"			
SP739/13800	85/F	See "Updated narratives for fesoterodine-treated subjects with nonfatal, treatment-emergent SAEs"			
Updated narratives for fesoterodine-treated subjects who dropped out due to eye disorders					
SP669/11238	57/F	Dry eye	8mg	Moderate	
SP669/13185	60/F	Eye irritation	8mg	Mild	
SP669/13186	55/F	Dry eye	8mg	Moderate	
Updated narratives for fesoterodine-treated subjects who dropped out due increase in transaminases					
None					

AE=adverse event, ECG=electrocardiogram, F=female, M=male, SAE=serious adverse event

Table 6. Discontinuations due to AE's (Study A0221007)

Subject number	Age/ gender	AE MedDRA Preferred Term/Investigator Term	Intensity	Outcome	Causality	SAE
Gastrointestinal disorders						
10061009	53/F	Dry mouth/Dry mouth	Severe	Resolved	Related	No
10021002	78/M	Constipation/Constipation	Moderate	Resolved	Related	No
10071008	62/F	Abdominal pain upper/Stomach pain	Moderate	Resolved	Related	No
10421006	77/F	Diarrhoea/Diarrhea	Mild	Resolved	Related	No
10441002	66/F	Nausea/Nausea	Moderate	Resolved	Related	No
10441005	66/F	Gastritis/Gastritis	Moderate	Resolved	Not Related	No
10471017	43/F	Abdominal pain upper/Gastrodynia	Severe	Resolved	Related	No
10751005	36/F	Oesophagitis/Oesophagitis	Mild	Continuing	Related	No
10801002	76/F	Dry mouth/Dry mouth	Severe	Resolved	Related	No
10811013	69/F	Dry mouth/Dry mouth	Severe	Continuing	Related	No
10811014	44/F	Constipation/Constipation	Severe	Continuing	Related	No
10821026	66/F	Constipation/Constipation Headache/Headache	Mild Mild	Resolved Resolved	Related Related	No No
10401004	68/M	Dyspepsia/Heartburn	Mild	Resolved	Not Related	No
10811023	44/F	Abdominal distension/Abdominal distension Dysuria/urination pain	Severe Severe	Resolved Resolved	Related Related	No
Infections and infestations						
10561004	45/F	Cystitis/Cystitis	Severe	Resolved	Related	No
10821012	62/F	Pyelonephritis acute/Acute pyelonephritis	Severe	Resolved	Not Related	Yes
Injury, poisoning and procedural complications						
10801010	71/F	Back injury/Back sprain	Mild	Resolved	Not Related	No
Investigations						
10031002	66/M	Blood glucose increased/High blood sugar	Moderate	Resolved	Related	No
Metabolism and nutrition disorders						
10361005	73/F	Dehydration/Dehydration	Severe	Resolved	Related	No
10371003	51/F	Fluid retention/Fluid retention	Moderate	Resolved	Related	No
Musculoskeletal and connective tissue disorders						
10801004	41/F	Muscular weakness/Lower extremity motor weakness	Severe	Resolved	Not Related	Yes
Nervous system disorders						
10331003	37/F	Dysgeusia/Metal taste in mouth	Moderate	Resolved	Related	No
10351002	76/F	Balance disorder/Loss of balance Oedema peripheral/edema of left leg	Moderate Mild	Resolved Resolved	Related Related	No No
10821020	56/F	Headache/Headache	Mild	Resolved	Related	No
10841009	42/F	Dizziness/Dizziness Headache/Headache	Moderate Moderate	Resolved Resolved	Related Related	No No
Psychiatric disorders						
10021012	49/F	Euphoric mood/High feeling	Moderate	Resolved	Related	No
10821013	60/F	Insomnia/Insomnia	Severe	Resolved	Related	No

Table 6 continued. Discontinuations due to AE's (Study A0221007)

Subject number	Age/ gender	AE MedDRA Preferred Term/Investigator Term	Intensity	Outcome	Causality	SAE
Renal and urinary disorders						
10361002	76/F	Urinary retention/Urinary retention	Moderate	Continuing	Related	No
10411002	79/F	Urinary retention/Acute urinary retention	Moderate	Resolved	Related	No
10801021	69/M	Dysuria/Voiding difficulty	Severe	Resolved	Related	No
10821024	44/M	Dysuria/Voiding difficulty	Mild	Resolved	Related	No
10821025	61/M	Dysuria/Voiding difficulty	Moderate	Resolved	Related	No
Reproductive system and breast disorders						
10551003	41/F	Genital haemorrhage/Transvaginal bleeding	Mild	Resolved	Not Related	No
Respiratory, thoracic and mediastinal disorders						
10091013	56/F	Cough/Dry cough	Mild	Resolved	Related	No
Skin and subcutaneous tissue disorders						
10751002	60/F	Hyperhidrosis/Hyperhidrosis	Moderate	Continuing	Related	No
Vascular disorders						
10551002	66/F	Hypertension/High blood pressure	Mild	Continuing	Not Related	No

Reviewer's Comment: The vast majority of AEs leading to discontinuation appear to be related to the anticholinergic properties of fesoterodine. All these AE discontinuation cases, including cases of euphoric mood and insomnia, will be reviewed in greater detail.

4. Summary

After a brief overview of the Safety Update, the adverse event profile in these studies appears to be consistent with the known characteristics of fesoterodine, and similar to that seen in the original NDA and the 120-day Safety Update.

According to the Sponsor, the most frequently reported adverse events (AE's) were consistent across the studies. The majority of the common AE's reported (e.g., dry mouth, urinary tract infection, constipation, and headache) were reported at much lower incidences in the shorter-term Pfizer study, as were the incidences of SAE's and premature discontinuations.

Causality for the 6 reported deaths as assessed by the investigator was considered unlikely related to study drug in 5 cases. In one additional case, the relationship to fesoterodine was not assessable.

Reviewer's Comment: There do not appear to be any new safety signals in this Final Safety Update compared to the original NDA. The safety profile of fesoterodine appears consistent with its pharmacologic activity as an

anticholinergic. Nonetheless, the possibly-related SAEs and AEs leading to study discontinuation will be reviewed in greater detail.

5. Recommended Regulatory Action

The Clinical review will continue. The following two Clinical comments should be conveyed to the Sponsor via regulatory letter:

1. *In your safety update, serious adverse events judged by the investigator as being at least possibly related to fesoterodine included: constipation, electrocardiogram QT prolonged, spontaneous abortion, and severe headache/nausea (one patient each). These cases will be reviewed in greater detail.*

2. *In your safety update, all cases of discontinuation due to AEs, including cases of euphoric mood and insomnia (one patient each), will be reviewed in greater detail.*

Harry Handelsman, DO
Medical Officer
Division of Reproductive and Urologic Products, DRUP

Mark Hirsch, MD
Medical Team Leader
DRUP

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

/s/

Harry Handelsman
7/3/2008 03:03:47 PM
MEDICAL OFFICER

Mark S. Hirsch
7/3/2008 03:05:30 PM
MEDICAL OFFICER
I concur.

NDA 22-030

Medical Team Leader's Memorandum: New NDA

Date Submitted:	March 17, 2006
Date Received:	March 27, 2006
PDUFA Goal Date:	January 27, 2007
Memo Completed:	January 25, 2007
Sponsor:	Schwarz Pharma LLC Raleigh, North Carolina
Drug Product:	Fesoterodine fumarate
Tradename:	[redacted] b(4)
Doses:	4mg and 8mg once daily
Route and formulation:	Oral extended-release tablet
Indication:	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency.

1. Executive Summary

The purpose of this memo is to convey my recommendation for regulatory action on this new drug application. I recommend an **Approveable** (AE) action, based upon a single unresolved Chemistry, Manufacturing and Controls (CMC) deficiency:

> Pre-Approval Inspection (PAI) of the active pharmaceutical ingredient (API) manufacturing facility, Schwarz Pharma Ltd., located in Shannon, Ireland could not be conducted because, as stated in the Sponsor's letter, dated July 20, 2006, this site would not be available for PAI until after the PDUFA date of January 27, 2007.

The following information is needed to address this deficiency:

> Satisfactory inspection of the API manufacturing facility, Schwarz Pharma Ltd., located in Shannon, Ireland, is required before this application may be approved.

In addition, agreement on final labeling has not been reached. While labeling discussions have ensued in a productive fashion, and the draft professional package insert (PI) contains the critical information needed for safe and effective use of the product, some additional discussion is needed to finalize agreement. Therefore, I advise that labeling resume in the next cycle, with the Division's revised labeling of January 19, 2007, serving as the basis for the next round of discussions. This should be noted in the AE action letter.

Otherwise, there are no unresolved clinical, statistical, clinical pharmacology, or nonclinical NDA review issues. Evidence presented in the application supports the clinical benefit of [redacted] 4mg and 8mg daily in ameliorating the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency and frequency, in an appropriate patient population, using the standard diary-based endpoints. Further, the b(4)

application provided evidence that the safety profile of ——— is similar to other oral anticholinergic medications for OAB, and is acceptable in relation to the demonstrated clinical benefit when used as directed in the current draft labeling. The reader should be aware that fesoterodine is rapidly and extensively metabolized to an active metabolite referred to as SPM 7605 (or 5-hydroxytolterodine), and this is also the major active metabolite of the approved drug Detrol. b(4)

2. Clinical Efficacy

2.1. Summary Efficacy Comments

In the final Clinical review dated January 17, 2006, Dr. Kaul conveyed these conclusions regarding the efficacy of ——— b(4)

- *"Fesoterodine showed a statistically significant and clinically meaningful improvement in decreasing the number of micturitions during an average 24 hour period when compared to placebo over a treatment period of 12 weeks in both SP583 and SP584 trials."*
- *"For incontinence episode frequency, there was a clinically meaningful decrease shown in both pivotal studies and the improvements were statistically significant when compared to placebo."*
- *"Both the pivotal studies SP583 and SP584 were adequate and well-controlled studies conducted in Europe and the United States, respectively. Both provide substantial evidence of efficacy in the primary and key secondary efficacy variables."*

The final Biometrics review corroborated the Clinical team's impressions. Dr. Sobhan's final review of January 10, 2007, concluded:

> *"Based on the efficacy data submitted from the two Phase 3 studies, our analysis showed that at Week 12, compared with placebo, both doses of ——— (4 and 8mg) significantly (P<.05) reduced the average number of micturitions and urge incontinence episodes."* b(4)

2.2. Phase 3 Study Designs

The Sponsor conducted two, Phase 3, efficacy and safety studies in support of the overactive bladder indication (SP583 in Europe and SP584 in the United States). These studies were designed in collaboration with DRUP reviewers and discussed at an End-of-Phase 2 meeting. There were designed in the usual standard fashion for the OAB indication; that is, they were both randomized, double-blinded, placebo-controlled, fixed-dose, parallel-arm studies comparing ——— 4mg daily and ——— 8mg daily to placebo for a treatment interval of 12 weeks in a well-defined OAB population. The co-primary endpoints were: b(4)

a) change-from-baseline in the average number of micturitions per 24 hours, and
b) change-from-baseline in the average number of urge urinary incontinence episodes per 24 hours.

A key secondary endpoint was the average volume voided per micturition as measured over 24 hours during the routine periodic dairy period. In both studies, diary-based data on micturition frequency per 24 hours, urge incontinence episodes per 24 hours, and volume voided with each micturition was collected at baseline and again at Weeks 2, 8 and 12. Week 12 was the study endpoint. Diaries were recorded for 3 days and data for volume voided was collected for 24 hours.

Entry criteria required that patients have symptoms of overactive bladder for ≥ 6-months duration, as demonstrated by at least 8 micturitions per day, and at least 6 urinary urgency episodes or 3 urge incontinence episodes per 3-day diary period. Both studies enrolled a large number of patients and most of these patients completed the 12-week treatment interval.

2.3. Patient Demographics and Disposition

In study SP583, a total of 1135 patients were randomized and 1132 were treated: 279 with placebo, 265 with fesoterodine 4mg/day, 276 with fesoterodine 8mg/day and 283 with tolterodine 4mg/day. Most patients (>80% in any treatment group) completed the full 12 weeks of treatment. Most of patients (81%) were female. The mean patient age was 57 years with a range of 19 to 86 years.

In study SP584, a total of 836 patients were randomized and 832 patients were treated: 266 with placebo, 267 with fesoterodine 4mg/day and 267 patients with fesoterodine 8mg/day. Most patients (>80% in any treatment group) completed full 12 weeks of treatment. Most of the patients (76%) were female. The mean age was 59 years with a range of 21 to 91 years. A total of 9% of patients were poor metabolizers for CYP2D6 by genotyping.

2.4. Results for the Co-Primary Endpoints and Key Secondary Endpoint

The following three tables (Tables 1-3) were generated by the medical officer from the data in the Sponsor's study reports for Studies SP583 and SP584. Tables 1 and 2 describe the Sponsor's reported results for the primary efficacy endpoints: average number of micturitions per 24 hours and average number of urge incontinence episodes per 24 hours, respectively. Table 3 describes the Sponsor's reported results for the key secondary endpoint: average volume voided per micturition.

Table 1. Micturitions per 24 hours*

	Study SP-583			Study SP-584		
	Placebo (n=279)	**Feso 4mg (n=265)**	**Feso 8mg (n=276)**	**Placebo (n=266)**	**Feso 4mg (n=267)**	**Feso 8mg (n=267)**
Baseline	12.0(3.7)	11.6(3.2)	11.9(3.8)	12.2(3.7)	12.9(3.9)	12.0(3.3)
Endpoint	10.9(4.2)	9.8(3.1)	10.0(4.4)	11.2(3.4)	11.0(3.6)	10.1(3.2)
Change from baseline	-1.0(3.0)	-1.7(2.7)	-1.9(3.1)	-1.0(3.4)	-1.9(3.6)	-2.0(3.0)
p-value (vs. placebo)		P<0.001	P<0.001		P=0.032	P<0.001

*Data presented as Mean (SD). Sample size reflects number of patients at baseline. p-value derived from analysis of the variance test using baseline to endpoint difference and LOCF.

Table 2. Urge Incontinence Episodes per 24 hours*

	Study SP-583			Study SP-584		
	Placebo (n=211)	**Feso 4mg (n=199)**	**Feso 8mg (n=223)**	**Placebo (n=205)**	**Feso 4mg (n=228)**	**Feso 8mg (n=218)**
Baseline	3.7(3.1)	3.8(3.4)	3.7(2.9)	3.7(3.3)	3.9(3.5)	3.9(3.3)
Endpoint	2.5(3.5)	1.8(2.9)	1.4(2.5)	2.7(3.3)	2.1(3.2)	1.4(2.1)
Change from baseline	-1.2(3.3)	-2.1(2.7)	-2.3(2.4)	-1.0(2.7)	-1.8(3.1)	-2.4(2.8)
p-value (vs. placebo)		P=0.001	P<0.001		P=0.002	P<0.001

* Data presented as Mean (SD). Sample size reflects number of patients at baseline. P-value derived from analysis of the variance test using baseline to endpoint difference and LOCF.

Table 3. Volume Voided per Micturition*

	Study SP-583			Study SP-584		
	Placebo (n=279)	**Feso 4mg (n=265)**	**Feso 8mg (n=276)**	**Placebo (n=266)**	**Feso 4mg (n=267)**	**Feso 8mg (n=267)**
Baseline	150 (52)	160 (60)	154 (57)	159 (69)	152 (60)	156 (58)
Endpoint	160 (62)	187 (93)	188 (74)	168 (96)	170 (78)	189 (77)
Change from baseline	9.8 (44)	27 (70)	33.5 (54)	7.9 (69)	17 (61)	33 (63)
p-value (vs. placebo)		P=<0.001	P<0.001		P=0.15	P<0.001

*Data presented as Mean (SD). Sample size reflects number of patients at baseline. P-value derived from analysis of the variance test using baseline to endpoint difference and LOCF.

The data presented in Tables 1-3 demonstrates that fesoterodine 4 and 8mg administered once daily for 12 weeks improved the two primary and key secondary efficacy variables compared to placebo. All three key variables (change in the average number of micturitions per 24 hours, change in the average number of urge incontinence episodes per 24 hours, and volume voided) improved in a dose-responsive, statistically significant manner compared to placebo treatment.

One additional efficacy issue deserves mention. Sponsor conducted additional analysis of the two co-primary endpoints for change-from-baseline to Weeks 2, 4, and 8, although these were not the primary timepoints of interest. The Sponsor sought efficacy claims related to ' The Clinical and Biometrics review teams conducted separate analyses of each co-primary endpoint at Week 2. We determined that both doses (4mg daily and 8mg daily) showed statistically significant superiority to placebo for change-from-baseline to Week 2 for urge incontinence episode frequency (in both studies), Therefore, the labeling text allows this claim for urge incontinence episode frequency only. b(4)

Additionally, the reader should be aware that the recommended dosing regimen for will be a starting dose of 4mg in all patients. If tolerability allows, and efficacy necessitates, patients may be titrated up to the 8mg daily dose. The two Phase 3, placebo-controlled, efficacy studies were fixed-dose, parallel-arm studies. The 9-month, open-label extensions of these fixed-dose studies allowed for dose-titration based upon tolerability and efficacy. Despite the lack of a placebo-controlled, dose-titration efficacy study, the review team strongly supports the recommended dose-titration regimen primarily because safety will be enhanced and efficacy will not be compromised. Many patients will be well-managed at the low dose and some may require the higher dose. This is acceptable. b(4)

3. Clinical Safety

3.1 Summary Safety Comments

In the final Clinical review dated January 17, 2007, Dr. Kaul provided the following conclusions regarding the safety of

- *"The overall size of the safety database and overall evaluation of safety was adequate."*
- *"The reported adverse clinical events are similar to the known side effects of other approved anti-muscarinic drugs, including dry mouth, constipation, dry eyes and urinary retention. No significant cardiovascular, hepatic, hematologic or renal toxicities were identified."*

b(4)

- *"Most reported clinical adverse events were mild to moderate in severity and resolved without significant medical intervention. The anti-muscarinic adverse events observed in the pivotal trials (i.e., dry mouth, constipation and urinary retention) appeared to be dose-related."*

- *"A thorough clinical review of a small number of serious adverse events (SAEs) in studies SP583 and SP584 revealed no probable association with the use of fesoterodine."*

- *"The thorough QT safety assessment from study SP686 demonstrated no signal of any effect of fesoterodine on the QT interval at the clinical dose of 4mg once a day and at a supra-therapeutic dose of 28mg once a day."*

- *"No (frank) hepatotoxicity was reported in any trials of fesoterodine, although there were a few patients with mild increase in serum transaminase levels, but <3X ULN. There was no determination of a direct association between these increases in transaminase levels and fesoterodine."*

  Of note, the data for increased serum transaminases is shown as a clinical AE in the Adverse Reactions section of the label.

- *"(In the Phase 3 studies), a slight dose-dependent increase in mean pulse rate from baseline to end of treatment occurred in all the fesoterodine treatment groups. (In the thorough QT study), there was a mild-moderate increase in heart rate following treatment in the high dose group (the supratherapeutic dose of 28mg daily)."*

  Of note, the effect of [redacted] on heart rate is shown in the Electrophysiology section of the label, as follows: "[redacted] is associated with an increase in heart rate that correlates with increasing dose. In the study described above [redacted] when compared to placebo, the mean increase in heart rate associated with a dose of 4 mg/day and 28 mg/day of fesoterodine was 3 beats/minute and 11 beats/minute respectively. In the two, phase 3, placebo-controlled studies in patients with overactive bladder, the mean increase in heart rate compared to placebo was approximately 3-4 beats/minute in the 4 mg/day group and 3-5 beats/minute in the 8 mg/day group." b(4)

3.2. Extent of Patient Exposure

The safety of fesoterodine was evaluated in Phase 2 and 3 placebo-controlled, and open-label trials in a total of 2859 patients with overactive bladder. Safety data is primarily drawn from the 2288 patients with OAB who received [redacted] in those trials. Of the 2288 actively treated patients, 782 received [redacted] 4 mg per day, and 785 received [redacted] 8 mg per day in Phase 2 or 3 studies with treatment periods of 8 or 12 weeks. Others received [redacted] at higher and lower doses, including a dose of 12mg per day. Approximately 80% of these patients had >10 weeks exposure to [redacted] b(4)

A total of 1964 patients participated in the two, Phase 3, 12-week, placebo-controlled studies and their subsequent 9-month, open-label extensions. In the two "pivotal" Phase 3 studies combined, 554 patients received —— 4 mg per day and 566 patients received —— 8 mg per day. b(4)

Patients also received —— for longer durations in the 9-month, open-label extension phases of the two, Phase 3, "pivotal" studies. In all trials combined, 857, 691, and 354 patients received —— for at least 6 months, 1 year, and 18 months respectively. b(4)

Overall, therefore, the extent of exposure is adequate to determine the safety of —— in the target population for the proposed indication.

3.3. Overall Adverse Events (AEs)

The overall adverse events, as reported in the controlled and open-label study, are reflective of the anti-muscurinic pharmcologic effect of ——, and are similar to those reported for other oral antimuscurinic drugs for OAB. Commonly reported AE's that occurred more often in patients treated with fesoterodine than placebo included: dry mouth, constipation, urinary tract infection, dyspepsia, lacrimal disorder (dry eyes), dry throat, dysuria, and abdominal pain. b(4)

Table 4 below is derived from the Sponsor's Integrated Summary of Safety (ISS) and provides all adverse events reported in at least 2% of subjects in any fesoterodine treatment group from all controlled studies (Safety Pool S1).

Table 4.

Treatment-emergent adverse events reported by ≥2% of subjects in any fesoterodine treatment group (Pool S1)

Preferred term	Placebo N=780 n (%)	Feso 4mg/day N=782 n (%)	Feso 8mg/day N=785 n (%)	Feso 12mg/day N=222 n (%)	Tolt 4mg/day N=290 n (%)
Dry mouth	65 (8)	173 (22)	275 (35)	113 (51)	49 (17)
Headache	59 (8)	64 (8)	49 (6)	34 (15)	14 (5)
Constipation	19 (2)	28 (4)	47 (6)	18 (8)	8 (3)
Urinary tract infection	22 (3)	26 (3)	32 (4)	5 (2)	4 (1)
Dyspepsia	4 (<1)	12 (2)	25 (3)	6 (3)	5 (2)
Lacrimal disorder (dry eye)	1 (<1)	10 (1)	23 (3)	6 (3)	1 (<1)
Nausea	24 (3)	17 (2)	18 (2)	15 (7)	6 (2)
Dry throat	4 (<1)	8 (1)	17 (2)	14 (6)	3 (1)
Dysuria	8 (1)	12 (2)	16 (2)	8 (4)	3 (1)
Abdominal pain upper	8 (1)	11 (1)	16 (2)	7 (3)	3 (1)
Nasopharyngitis	23 (3)	28 (4)	13 (2)	7 (3)	10 (3)
Back pain	9 (1)	19 (2)	12 (2)	2 (<1)	1 (<1)
Diarrhea	16 (2)	18 (2)	11 (1)	6 (3)	3 (1)
Upper respiratory tract infection	16 (2)	16 (2)	10 (1)	3 (1)	2 (<1)
Influenza	19 (2)	25 (3)	7 (<1)	4 (2)	2 (<1)
Dizziness	18 (2)	17 (2)	9 (1)	8 (4)	4 (1)
Abdominal pain	13 (2)	6 (<1)	7 (<1)	8 (4)	5 (2)
Cough	13 (2)	17 (2)	8 (1)	6 (3)	5 (2)
Asthenia	6 (<1)	2 (<1)	5 (<1)	5 (2)	2 (<1)
Chest pain	5 (<1)	8 (1)	4 (<1)	5 (2)	1 (<1)
Dysgeusia	6 (<1)	4 (<1)	4 (<1)	7 (3)	0
Vision blurred	8 (1)	3 (<1)	4 (<1)	5 (2)	2 (<1)
Nasal dryness	3 (<1)	7 (<1)	3 (<1)	7 (3)	2 (<1)

Feso=fesoterodine, Tolt=tolterodine

These adverse events are commonly seen with the use of anti-muscarinic drugs. The initial onset of drug-related AE's generally occurred within the first month of treatment. Most AE's were mild or moderate in intensity. Severe AE's were reported for 4%, 5%, 8%, and 14% of patients in the placebo; and [redacted] 4, 8, and 12mg/day groups, respectively. Dry mouth was the AE most often rated as severe in intensity. Adverse events led to discontinuation in 6/780 (3%) in the placebo group; and 35/782 (5%), 45/785 (6%), and 27/222 (12%) patients in the [redacted] 4, 8, and 12mg/day groups respectively. The most common adverse event leading to discontinuation was dry mouth.

b(4)

With long-term fesoterodine treatment in the open-label extension studies, the profile of common AE's was similar to that listed above for Safety Pool S1. Similar to the controlled studies, most adverse events of dry mouth and constipation were mild to moderate in intensity, with only a few cases reported as severe. Specifically, with long-term treatment, severe AEs were reported for 14% of patients. Severe dry mouth (4%) and severe constipation (1%) were the only AEs reported as severe by ≥1% of patients during longer-term treatment. Serious adverse events reported by more than 2 patients each during the open-label extension studies included: myocardial infarction, bronchitis, cholecystectomy, knee arthroplasty, and breast cancer.

3.4. Deaths and Serious Adverse Events (SAEs)

As of the original submission of this NDA and all safety updates thereafter, a total of 6 deaths were reported. None of these deaths were judged by the investigator to be related to the study medication. Of these 6 patients who have died during this drug development program, one patient (in study SP582) died from cerebrovascular accident, the second patient (in study SP583) died from MI, the third patient (in study SP738) died due to metastastases to liver, the fourth patient (in study SP738) died due to "sudden death", the fifth patient died due to "unknown causes" several months after completing treatment (in study SP583), and the sixth patient died due to "natural causes" (in SP739). Five of the six deaths were considered by the investigators to be unrelated to festerodine. The "sudden death" case was considered "unlikely related".

In the controlled clinical trials combined, SAE's were reported in patients treated with placebo, fesoterodine 4mg, 8mg, or 12mg/day in 2%, 4%, 3%, and 6% of patients in these treatment groups, respectively. Serious AE's in all treatment groups occurred across multiple body systems with no obvious trends. Serious AEs reported by more than 1 patient in any fesoterodine-treated group included: chest pain/angina (in 3 patients), pneumonia, asymptomatic QTc interval prolongation as seen on ECG, appendicitis, and salpingitis (in 2 patients each). Other SAE types were reported in only 1 patient each.

During long-term open-label treatment, SAE's occurred in 9% of patients. Serious AEs reported by more than 2 patients each during open-label treatment included: myocardial infarction (in 4 patients [<1%]); and breast cancer, bronchitis, knee arthroplasty, and cholecystectomy (in 3 patients each).

3.5. Other Potential Safety Issues

3.5.1. Use In Combination With Potent CYP3A4 Inhibitors

The active metabolite of fesoterodine, SPM 7605, is metabolized by both CYP2D6 and CYP3A4. Therefore, the pharmacokinetic and clinical effect of strong inhibitors of CYP3A4 is of interest. Inhibition of CYP3A4 by the potent inhibitor ketoconozole increased SPM 7605 Cmax and AUC by approximately 2-fold and 2.4-fold, respectively. In a CYP2D6 poor metabolizer, the increases related to CYP3A4 inhibition are greater. For example, a dose of 8mg in a poor CYP2D6 metabolizer taking ketoconozale would produce similar exposures to 28mg in an extensive CYP2D6 metabolizer. While 28mg

was reasonably well tolerated in Phase 2 and in the thorough QT study, there was an increased incidence of dry mouth, urinary retention and increased heart rate. Analysis of adverse events in those patients who used CYP3A4 inhibitors during the Phase 3 clinical trials showed that users were somewhat more likely to report an AE from any system than those who did not use CYP3A4 inhibitors (62% vs 51%, respectively). The most notable differences between those who used CYP3A4 inhibitors and those who did not were: dry mouth (40% vs. 35%, respectively), constipation (9% vs. 5%, respectively), and urinary tract infection (10% vs. 5%, respectively). Taken together, it was determined that the maximum dose should be restricted to 4mg per day in patients taking concomitant potent inhibitors of CYP3A4, such as ketoconozole. The Sponsor agreed.

3.5.2. Use in Pregnancy

There are no adequate and well-controlled trials or data using fesoterodine in pregnant women. At exposures similar to and higher than those observed with the to-be-marketed doses, there was no definitive evidence of frank teratogenecity, but fetal resorptions, fetal losses, and a few cleft palates were observed in animal studies. These findings are similar to those for other drugs in the class and may be related to maternal stress due to the pharmacologic effects of the drug. Nevertheless, it was determined that the available information supported labeling as a Category C drug, to be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. The Sponsor agreed to this labeling.

3.5.3. Geriatric Use

As reflected in labeling and consistent with other anti-muscurinic agents for OAB, a modestly increased incidence of anticholinergic adverse effects were seen in patients aged 75 years and greater.

b(4)

The label recommends starting all patients on 4mg daily and titrating up only as tolerability allows. This is acceptable for all patients, including geriatric patients.

3.5.4. Pediatric Use

The safety and effectiveness of [Tradename] in pediatric patients have not been established. The Sponsor will be offered a waiver of pediatric studies for patients under 5 years of age and a deferral of studies for older pediatric patients.

4. Recommendations from Other Disciplines and Consultants

4.1. Clinical Pharmacology and Biopharmaceutics

In their final review, dated December 6, 2006, Drs. Tran and Kim, stated:

"This reviewer finds NDA 22-030 for fesoterodine fumarate acceptable from a Clinical Pharmacology perspective, provided the labeling comments are adequately addressed."

In regard to specific labeling comments, these were detailed on pages 63 to 76 of the Clinical Pharmacology review. The most important labeling revisions requested by Clinical Pharmacology included:

1. Addition of a specific table in the Clinical Pharmacology section summarizing pharmacokinetic parameters for SPM 7605 (fesoterodine's active metabolite) in poor and extensive cytochrome P450 2D6 (CYP2D6) metabolizers. A table was added by Sponsor.

2. Restriction of the —— dose to 4mg in patients taking concomitant potent inhibitors of the hepatic enzyme, CYP3A4. This restriction was added by Sponsor. b(4)

3. Addition of data on heart rate to the Electrophysiology section, showing the effect of —— on increasing heart rate at higher exposures. This information was added by Sponsor.

Clinically relevant comments from the Clinical Pharmacology review included:

1. Following oral administration, the parent compound fesoterodine cannot be detected in plasma and the pharmacokinetics of fesoterodine are described by those of its active metabolite SPM 7605. Fesoterodine itself is a weak muscurinic receptor antagonist, but SPM 7605 is a potent, non-selective, muscurinic receptor antagonist. SPM 7605 (or 5-hydroxymethyltolterodine) is the same chemical entity as the major metabolite of tolterodine (tradename Detrol). However, the parent tolterodine and 5-hydroxytolterodine both contribute to the antimuscurinic action of Detrol, while the parent fesoterodine is not detectable in plasma.

2. As an immediate release preparation, fesoterodine was rapidly absorbed, with the Tmax for SPM 7605 being approximately 1 hour. The IR drug was also rapidly cleared from the body, with an apparent terminal half-life of about 4 hours. Steady state is reached in 3 days —— fesoterodine was developed using an extended-release formulation —— The Tmax for the ER version is about 5 hours and the half-life is about 7-8 hours. —— is well absorbed and widely distributed. Pharmacokinetics for the ER appear to be proportional over the approved dose range and up to 28mg. All metabolites are excreted in the urine and urinary excretion accounts for 70% of the total clearance. Excretion in the feces is lower (approximately 7%). b(4)

3. Pharmacodynamic analyses demonstrated a positive dose-efficacy response for the primary and key secondary endpoints in the Phase 3 studies. There was also a

positive dose-safety responses relationship for the adverse events of dry mouth, constipation, and increased heart rate for the fesoterodine 4mg and 8mg/day doses.

4. In regard to the intrinsic and extrinsic factor effects on the PK of SPM 7605:

    a. Gender, age and race had no significant effect on the pK of fesoterodine.

    b. Moderate hepatic impairment increased SPM 7605 Cmax and AUC by 1.4-fold and 2.1-fold, respectively. No dose adjustment is needed in this circumstance. Since severe hepatic impairment was not studied, fesoterodine will not be recommended for use in such patients.

    c. Mild renal insufficiency increased SPM 7605 Cmax and AUC by 1.3-fold and 1.6-fold, respectively. Moderate renal insufficiency increased SPM 7605 Cmax and AUC by 1.5-fold and 1.8-fold, respectively. Severe renal insufficiency increased SPM 7605 Cmax and AUC by 2.0-fold and 2.3-fold, respectively. There is no clinical data in patients with severe renal insufficiency. While no dose adjustment is required in patients with mild or moderate renal insufficiency, the dose is restricted to 4mg daily in patients with severe renal insufficiency.

    d. SPM 7605 is metabolized primarily by CYP2D6 and CYP3A4. Therefore, the effect of CYP 2D6 metabolizer status was examined. Poor metabolizers of CYP 2D6 (who constitute approximately 8% of the general U.S. population) had Cmax and AUC values that were approximately 2-fold those of CYP2D6 extensive metabolizers. No dose adjustment is recommended for poor CYP2D6 metabolizers. The reader should also note that ——— is to be initiated at the lowest approved dose (4mg daily) and dosage is to be increased in an individual patient only as tolerability allows and efficacy necessitates. b(4)

    e. Inhibition of CYP3A4 by the potent inhibitor ketoconozole increased SPM 7605 Cmax and AUC by approximately 2-fold and 2.4-fold, respectively. However, the reader should be aware that the dose of 8mg in a poor CYP2D6 metabolizer taking ketoconozale would produce similar exposures to 28mg in an extensive CYP2D6 metabolizer. While this dose was reasonably well tolerated in Phase 2 studies and in the thorough QT study, there was an increased incidence of dry mouth, urinary retention and increased heart rate. Therefore, it was recommended (and Sponsor agreed) to restrict the maximum dose of ———to 4mg/day in patients taking concomitant potent inhibitors of CYP3A4, such as ketoconozole. b(4)

5. Then issue of potential "dose-dumping" in the presence of alcohol was considered by the review team. Human studies in this regard were determined to be unnecessary because the in vitro dissolution data showed that the ——— b(4)

formulation was generally "nondisintegrating", and there were no serious or life-threatening adverse events reported at doses of 16mg IR or 28mg ER.

6. There were six (6) ER formulations of during its development. b(4)
Formulations D and E were used in the Phase 3 studies. Formulation F is the to-be-marketed formulation. Changes from D/E to F were minor and successfully bridged by in vitro dissolution data. Most pK studies used Formulation B, which was successfully bridged to Formulation F with an in vivo bioequivalence study and demonstration of dose proportionality of B and F. Finally, Formulation F had a Level 2 manufacturing change and that was successfully bridged by similarity of in vitro dissolution profiles.

4.2. Pharmacology/Toxicology

In their final review dated December 12, 2006, Drs.McLeod-Flynn and Reid stated:

> *"There is no impediment to approval of this NDA from a pharmacology/toxicology perspective."*

In regard to labeling, the Pharmacology team recommended extensive changes to the following subsections of the Precautions section: "Carcinogenesis, Mutagenesis, Impairment of Fertility", "Pregnancy" and "Nursing Mothers". The Sponsor accepted these recommendations in large part. They included:

1. Revising exposure multiples in the Carcinogenesis section
2. Providing clearer and more specific summary results for mice and rabbit reproductive toxicology studies, as follows:
   a. b(4)
   b. b(4)

b(4)

3.

Clinically relevant comments from the Pharmacology/Toxicology review included:

1. Exaggerated pharmacological effects (including mydriasis, increased heart rate and neurological effects) were the primary limiting toxicity for both mice and dogs. Dr. McLeod notes that these effects were further characterized in humans (see Clinical Safety).
2. No treatment-related histopathology was observed up to 6 months in mice and 9 months in dogs.
3. QT effects were not seen in dogs administered oral fesoterodine, but were seen at dogs given intravenous fesoterodine at >10 times the expected clinical exposure. Dr. McLeod notes that these effects were further characterized in humans (see Clinical Safety).
4. Two-year carcinogenecity studies were negative in rats and mice for up to 2 years at the maximum tolerated dose.
5. Low multiples of expected clinical exposures were observed for some reproductive effects in animals including cleft palate (as labeled above), but Dr. McLeod notes that "there is a history of similar effects in animals for anti-muscurinic drugs for overactive bladder, including tolterodine which produces the same active metabolite as fesoterodine". She continues: "Several effects reported in animals, such as cleft palate in mice, are reported to be associated with stress during the gestational period." In regard to these reproductive toxicology findings, the PharmTox team concluded that: "Although fesoterodine is not used at doses which are expected to cause stress in humans, labeling should recommend that it should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus." (Category C)

   While there are no human studies investigating this issue, a search of the FDA's Adverse Event Reporting System (AERS) database revealed no cases of teratogenecity in association with tolterodine, a widely used anti-muscurinic for OAB which produces the same active metabolite as fesoterodine.

Dr. Reid's Pharmacology Team Leader's memo provided the following conclusion and summary comments on labeling

> "*From a pharmacology/toxicology perspective, the drug appears well-characterized and there are no nonclinical findings which would indicate that this drug should not be approved for the chronic treatment of overactive bladder in adults.*"

"I concur with the recommended labeling changes proposed by the primary reviewer, Dr. McLeod-Flynn. I concur with labeling under Pregnancy Category C due to drug-related adverse effects observed on fetal viability in both mice and rabbits, but no definitive frank teratogenecity, and delayed development in offspring exposed in utero."

4.3. Biometrics

In their final review, dated January 10, 2007, Drs. Sobhan and Kammerman stated:

"Based on the efficacy data submitted from the two Phase 3 studies, our analysis showed that at Week 12, compared with placebo, both doses of [redacted] (4 and 8mg) significantly (P<.05) reduced the average number of micturitions and urge incontinence episodes."

Clinically relevant comments from the Biometrics review included:

1. Biometrics performed statistical analyses with respect to the two protocol-specified co-primary endpoints for both Phase 3 studies (SP583 and SP584). The analysis supported the Sponsor's claims of efficacy for the Week 12 primary endpoint for both doses in both studies.

2. The sample size was adequate for testing the superiority hypothesis for both co-primary efficacy endpoints for both studies. The use of a hierarchical closed-testing procedure was appropriate for controlling Type I error with regards to the co-primary endpoints.

3. No hierarchical plan was in the protocol for testing secondary endpoints (e.g. average volume voided) or for testing the co-primary endpoints at different Weeks (e.g. Week 2, Week 4, Week 8, etc). Biometrics went ahead and preformed analyses of some secondary endpoints and the co-primary endpoints at different weeks, not because these were pre-specified in the protocol, but rather because the Sponsor made labeling claims for these and because some of these were determined to be clinically important by the medical officer team. For example, one of the secondary endpoints (average volume voided) is assessed in all OAB Phase 3 studies (and appears in most labels), and efficacy at earlier timepoints is of clinical interest to practitioners and patients. In order to conduct statistical analyses of "volume voided" and efficacy at earlier timepoints, Biometrics needed to use "other methods".

4. For change-from-baseline in average volume voided, [redacted] 4 and 8mg were both statistically superior to placebo in SP583, using ANCOVA with factors for treatment and site. However, only the 8mg dose was statistically superior to placebo in SP584. Sponsor agreed that the 4mg dose was not statistically superior to placebo in this trial (p=0.24). b(4)

5. For change-from-baseline to Week 2 (a claim made by the Sponsor), in Study 583, both doses of [redacted] were statistically better than placebo for the incontinence episode endpoint. [redacted] b(4)

For change-from-baseline to Week 2 in Study 584, both doses of [redacted], were again statistically better than placebo for the incontinence episode endpoint. [redacted] b(4)

The proposed labeling has been revised accordingly and Sponsor has agreed.

4.4. Chemistry (Pre-Marketing Drug Quality)

In their final CMC review, Drs. Agarwal and Rhee stated:

> *"The application is approvable from Chemistry, Manufacturing and Control standpoint based upon the WITHHOLD recommendation from the Office of Compliance for the drug substance manufacturing site in Ireland, and some labeling issues."*

This deficiency is based upon the final "Withhold" recommendation from the Office of Compliance for this application. The reason for this Compliance recommendation is that the drug substance manufacturing site in Ireland is not ready for inspection.

Chemistry also noted several remaining "labeling issues". These were conveyed to Sponsor on January 17, 2006: b(4)

- [redacted]
- Replace the word "Tradename" with [redacted] in the PI and PPI.
- In the "How Supplied" section, correct the NDC numbers for the blister labels.
- In the "How Supplied" section, identify the number of tablets in the "Unit Dose Blisters".

The Sponsor responded to these issues by agreeing to all four but [redacted]

The following summary comments from the Chemistry reviewer provide further information or [redacted] b(4)

1. [redacted] is oval in shape, film-coated, engraved on one side with an [redacted] The 4mg tablet is light blue and the 8mg tablet is blue.
2. [redacted] tablets are manufactured by Schwarz Pharma Manufacturing Inc in Germany and tested, package and labeled by Schwarz Pharma in the United States.
3. [redacted] is an extended release tablet that uses [redacted] b(4)

4. Based upon the Sponsor's agreement to tighten the impurity specification, the acceptance criteria for the drug product are now all satisfactory.
5. A 24-month shelf-life is acceptable.
6. The tradename [redacted] is acceptable.
7. [redacted] is packaged in bottles and in blisters. The blister contains 7 to 14 tablets per card, and the bottles will contain 30 or 90 tablets. Bottles contain child-resistant closure caps.

4.5. Division of Scientific Investigations (DSI)

In their final consultative review, dated January 18, 2007, Drs. Blay and Lewin provided the following overall assessment and recommendation:

> *"The inspections of Drs. Elliot, Arpo, and Timberg did not identify any significant regulatory violations. Overall, the data appear acceptable in support the respective indication. This assessment and recommendation for Drs. Arpo and Timberg are based solely upon the review of the Form FDA 483s. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.*
>
> *The inspection of Dr. Bergner revealed deficiencies with diary entries for seven of 17 subjects and the determination of residual urine volumes for four of sixteen subjects. Given the extent of these deficiencies, the review Division may wish to consider whether to exclude these data from its safety or efficacy analyses."*

The DSI summary assessment was based on the following factors:

1. Four sites (2 for each pivotal trial) were selected for routine inspection because they were the largest enrollers. For Study SP583, Drs. Bergner (Clearwater, Florida) and Elliot (Evansville, Indiana) were inspected, and for Study SP584, Drs. Arpo (Tallinn, Estonia) and Timberg (Tartu, Estonia) were inspected.

2. For Dr. Elliot's site (Evansville), the only deviation was that two patients were randomized who would have met the exclusion criterion for polyuria. The data from this site was acceptable.

3. For Dr. Bergner's site (Clearwater), there were seven subjects where the study diaries were not completed properly. The diary errors included: blanks, deletions or revisions without explanation, repetition of data for multiple days, and data that was not physiologically probable (multiple micturitions for Day 1 and none for Day 2). In addition, four subjects had baseline residual urine volumes that were unclear and may have caused these subjects to be excluded. DSI concluded that the data from those 7 subjects appeared unacceptable and advised that DRUP carefully consider whether to include or exclude that data. The remainder of the data from this site was otherwise without noted specific deficiency. The DRUP Clinical review team and Biometrics reviewer believe that the Phase 3 trials include so many patients and the statistical evidence is so compelling in favor of the product, that excluding the data from these 7 patients would have little impact on the overall efficacy conclusions.

4. For Dr. Timberg's site (Tallinn, Estonia), there were no violations or deviations listed in the Form FDA 483.

5. For Dr. Arpo's site (Tartun, Estonia), there was a single deviation, where one patient with severe diarrhea had the event listed in the source data but not on the CRF. The rest of the inspection was acceptable.

4.6. Division Medication Errors and Technical Support (DMETS)

In their final review dated January 11, 2007, Drs. Pincock, Roselle, Toyer and Ms. Holmquist, provided the following summary statement:

> *"DMETS has no objections to the use of the proprietary name, ——— This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA."*

b(4)

b(4)

DMETS also made recommendations on the container labels, cartons and insert labeling. The most critical of these was the recommendation that the ——— This was conveyed to Sponsor, who agreed to ——— This was acceptable.

b(4)

DMETS also made several minor comments re: specific font size and labeling details. These were acknowledged and managed by our Chemistry review team in consultation with the Clinical team.

4.7. Division of Drug Marketing, Advertising and Communications (DDMAC)

In her eMAIL correspondence dated January 4, 2006, Corrinne Kulick of DDMAC provided detailed comments on product labeling from a marketing and advertising perspective.

The DRUP Clinical review team evaluated each of Ms. Kulick's 19 comments. Some of these were incorporated as labeling revisions and others were not. Examples of labeling revisions that were requested in light of the DDMAC comments included: clarifying the extent of patient exposure in the Adverse Reactions section, describing serious adverse events in more detail in the Adverse Reactions section, and defining the patient population better in the Clinical Studies subsection.

Therefore, all DDMAC comments were carefully considered and acted upon as deemed appropriate by DRUP.

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/s/

Mark S. Hirsch
1/25/2007 09:15:42 AM
MEDICAL OFFICER