CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-030

CROSS DISCIPLINE TEAM LEADER REVIEW

NDA 22-030

Cross-Discipline Team Leader's Memorandum

Date Submitted: May 1, 2008
Date Received: May 2, 2008
Date Memo Completed: October 19, 2008

Drug: Toviaz (fesoterodine fumarate)
Dose, Route and Formulation: 4mg and 8mg oral extended-release tablets
Regimen: Once daily
Indication: Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency and frequency.

1. Executive Summary

The purpose of this memorandum is to provide the Division Director with my recommendation for regulatory action on this new drug application. I recommend **approval** of this application.

On January 25, 2007, this application received an Approvable action. The fundamental deficiency that led to the Approvable action was a Chemistry issue; specifically, Pre-Approval Inspection (PAI) of the active pharmaceutical ingredient (API) manufacturing facility located in Shannon, Ireland could not be conducted because this site was not available for PAI prior to the original PDUFA goal date. In the January 25, 2007, Approvable letter, the Agency stipulated that a satisfactory inspection of the API manufacturing facility was required prior to approval of this application. During this second cycle, the API site was inspected and Compliance and Chemistry found the site to be acceptable.

In addition to the Chemistry issue, the Approvable letter noted that agreement on final labeling had not been reached. During this cycle, productive labeling discussions resulted in successful agreement on the professional package insert (PI), the patient package insert (PPI), and all container/carton labeling.

Finally, the January 25, 2007, Approvable letter stated that another Safety Update would need to be submitted with the Complete Response, to include data from all nonclinical and clinical fesoterodine studies since the previous Safety Update. The Safety Update included new safety data since the cutoff date of the original NDA from 3, open-label, long-term extension studies completed by Schwarz Pharma (Studies SP669, SP738, and SP739), and a 12-week, open-label study conducted by Pfizer (Study A0021007). In addition, new safety data was submitted from 4 new Phase 1 studies. According to the medical officer's review, as well as my secondary Clinical review, the safety profile of fesoterodine is acceptable and remains unchanged compared to that described in the original NDA and the original 120-Safety Update. No new risks or safety issues have been identified.

Therefore, all three deficiencies in the Approvable letter have been fully addressed and are resolved. Final agreements have been reached with Sponsor on all labeling. There are no remaining deficiencies for this application and it may be approved.

The remainder of this memo provides:

1. Overviews of efficacy and safety results from the original application. For additional details, the reader is referred to my original cross-discipline team leader's memo dated January 25, 2007 as well as Dr. Suresh Kaul's primary medical officer's review of the original application.

2. An overview of the safety information provided in this most recent Safety Update. For additional details the reader is referred to Dr. Harry Handelsman's primary medical officer's review dated October 7, 2008.

3. An overview of the recommendations and comments from each of the other disciplines and consultants, as derived from team meetings and the finalized reviews of each discipline and consultant.

2. Overview of Efficacy Results (Original NDA)

As outlined in my previous CDTL memo, the Sponsor conducted two, Phase 3, efficacy and safety studies in support of the overactive bladder indication (Study SP583 in Europe and Study 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 Toviaz 4mg daily and Toviaz 8mg daily to placebo for a treatment interval of 12 weeks in a well-defined OAB population. The co-primary endpoints were:

- change-from-baseline in the average number of micturitions per 24 hours, and
- 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 $\geq$ 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.

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.

Results for the primary endpoints and for mean change in voided volume per micturition from the two 12-week clinical studies of Toviaz are reported in Table 1. Data for the tolterodine arm in Study SP583 is not shown.

Table 1. Mean baseline and change from baseline to Week 12 for urge urinary incontinence episodes, number of micturitions, and volume voided per micturition

	Study SP583			Study SP584		
Parameter	**Placebo N=279**	**Toviaz 4mg/day N=265**	**Toviaz 8mg/day N=276**	**Placebo N=266**	**Toviaz 4mg/day N=267**	**Toviaz 8mg/day N=267**
Number of urge incontinence episodes per 24 hours[a]						
Baseline	3.7	3.8	3.7	3.7	3.9	3.9
Change from baseline	-1.20	-2.06	-2.27	-1.00	-1.77	-2.42
p-value vs placebo	-	0.001	<0.001	-	<0.003	<0.001
Number of micturitions per 24 hours						
Baseline	12.0	11.6	11.9	12.2	12.9	12.0
Change from baseline	-1.02	-1.74	-1.94	-1.02	-1.86	-1.94
p-value vs placebo	-	<0.001	<0.001	-	0.032	<0.001
Voided volume per micturition (mL)						
Baseline	150	160	154	159	152	156
Change from baseline	10	27	33	8	17	33
p-value vs placebo	-	<0.001	<0.001	-	0.150	<0.001

vs=versus

a Only those patients who were urge incontinent at baseline were included for the analysis of number of urge incontinence episodes per 24 hours: In Study 1, the number of these patients was 211, 199, and 223 in the placebo, Toviaz 4 mg/day and Toviaz 8 mg/day groups, respectively. In Study 2, the number of these patients was 205, 228, and 218, respectively.

The data presented in Table 1 demonstrates that fesoterodine 4mg 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 manner compared to placebo treatment. Comparisons to placebo for both doses for each endpoint were statistically significant except for volume voided per micturition in Study SP584.

The Biometrics review of the original NDA corroborated these results. 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 [redacted] (4 and 8mg) significantly (P<.05) reduced the average number of micturitions and urge incontinence episodes."*

b(4)

A reduction in the number of urge urinary incontinence episodes per 24 hours was observed for both Toviaz doses as compared to placebo as early as two weeks after starting blinded study medication.

Finally, it is important to point out that the recommended dosing regimen for Toviaz 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.

3. Overview of Safety Results (Original NDA)

In the medical officer's review for the original NDA, the Clinical review team drew the following conclusions about the safety of Toviaz:

- The reported adverse clinical events for Toviaz are similar to the known side effects of other approved anti-muscarinic drugs, including dry mouth, constipation, dry eyes and urinary retention.
- 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.
- 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).

  The effect of Toviaz on heart rate is shown in the Electrophysiology section of the label, as follows: "Toviaz is associated with an increase in heart rate that correlates with increasing dose. In the study described above (the TQT study), 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."

According to the original NDA, the safety of fesoterodine was evaluated in Phase 2 and 3 trials in a total of 2859 patients with overactive bladder. Safety data was primarily drawn from the 2288 patients who received Toviaz. Of these, 782 received Toviaz 4 mg per day, and 785 received Toviaz 8 mg per day in treatment periods of 8 or 12 weeks. Other patients in the clinical development program received Toviaz at higher and lower doses, including a dose of 12mg per day, and approximately 80% of those patients had at least 10 weeks exposure to Toviaz.

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 Toviaz 4 mg per day and 566 patients received Toviaz 8 mg per day.

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

In the original NDA, a total of 6 deaths were reported. Of these, one patient died from cerebrovascular accident, the second patient died from MI, the third patient died due to metastastases to liver, the fourth patient died due to "sudden death", the fifth patient died due to "unknown causes" several months after completing treatment, and the sixth patient died due to "natural causes". 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, serious adverse events (SAE's) were reported in patients treated with placebo, fesoterodine 4 mg/day and fesoterodine 8mg/day in 2%, 4% and 3% of patients, 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, electrocardiocardiogram QTc interval prolongation, appendicitis, and salpingitis (in 2 patients each). All other SAE types were reported in 1 patient each.

In the original NDA, 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.

Table 2 lists adverse events, regardless of causality, that were reported in the combined Phase 3, randomized, placebo-controlled trials at an incidence greater than placebo and in 1% or more of patients treated with Toviaz 4 or 8 mg once daily for up to 12 weeks.

Table 2. Adverse events with an incidence exceeding the placebo rate and reported by ≥1% of patients from double-blind, placebo-controlled Phase 3 trials of 12 weeks treatment duration

System organ class/Preferred term	Placebo N=554 %	Toviaz 4mg/day N=554 %	Toviaz 8mg/day N=566 %
Gastrointestinal disorders			
Dry mouth	7.0	18.8	34.6
Constipation	2.0	4.2	6.0
Dyspepsia	0.5	1.6	2.3
Nausea	1.3	0.7	1.9
Abdominal pain upper	0.5	1.1	0.5
Infections			
Urinary tract infection	3.1	3.2	4.2
Upper respiratory tract infection	2.2	2.5	1.8
Eye disorders			
Dry eyes	0	1.4	3.7
Renal and urinary disorders			
Dysuria	0.7	1.3	1.6
Urinary retention	0.2	1.1	1.4
Respiratory disorders			
Cough	0.5	1.6	0.9
Dry Throat	0.4	0.9	2.3
General disorders			
Edema peripheral	0.7	0.7	1.2
Musculoskeletal disorders			
Back pain	0.4	2.0	0.9
Psychiatric disorders			
Insomnia	0.5	1.3	0.4
Investigations			
ALT increased	0.9	0.5	1.2
GGT increased	0.4	0.4	1.2
Skin disorders			
Rash	0.5	0.7	1.1

ALT=alanine aminotransferase, GGT=gamma glutamyltransferase

Most AE's were mild or moderate in intensity. Severe AE's were reported for 4%, 5%, and 8% of patients in the placebo, Toviaz 4 mg/day, and Toviaz 8 mg/day groups, respectively. Dry mouth was the AE most often rated as severe in intensity. Adverse events led to discontinuation in 3%, 5%, and 6% of patients in the placebo, Toviaz 4 mg/day and Toviaz 8 mg/day groups respectively. The most common adverse event leading to discontinuation was dry mouth.

Finally, with long-term fesoterodine treatment in the open-label extension studies, in the original NDA, the profile of common AE's was similar to that listed in Table 2 above. 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.

There are several additional special safety issues and these are delineated individually in the original CDTL memo. One notable finding was a modestly increased incidence of anticholinergic adverse effects in patients aged 75 years and greater compared to patients younger than 75 years. Of 1120 patients who received Toviaz in the two Phase 3, 12-week, placebo-controlled, efficacy and safety studies, 373 (33%) were 65 years of age or older, and 123 (11%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between patients younger than 65 years of age and those 65 years of age or older in these studies; however, the incidence of commonly reported anticholinergic adverse events (constipation, urinary tract infection and dizziness) was higher in patients 75 years of age and older as compared to younger patients. This information has been added to the label. In addition, the label recommends starting all patients on 4mg daily and titrating up as tolerability allows and efficacy necessitates. This is acceptable for all patients, including geriatric patients.

4. Overview of Safety Results from the Final Safety Update

The Complete Response included a substantive Final Safety Update, which was reviewed in detail by the primary medical officer, Dr. Harry Handelsman. The reader is referred to Dr. Handelsman's review for additional details. An overview of results from the Safety Update is provided here.

4.1 Contents of the Safety Update

The final update included 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 from an ongoing 12-week, open-label study (A0021007), initiated by Pfizer, with data included as of January 1, 2008. In addition, the Complete Response included summaries of safety from one new Phase 1 study completed by Schwarz Pharma (Studies SP857) and three new Phase1 studies conducted by Pfizer (Studies A0221004, A0221015 and A0221044) since the NDA.

4.2 Extent of Exposure in the Safety Update and Disposition of Subjects

The extent of exposure to fesoterodine in the original NDA and final Safety Update is substantial. Overall, 2288 subjects received fesoterodine in the Phase 2 and 3 studies, and another 525 received fesoterodine in the Phase 1 studies. In all fesoterodine studies

conducted by Schwarz Pharma combined, including the original NDA studies, their open-label extensions, and the additional Phase 1 study since the NDA, a total of 857 patients, 701 patients, 615 patients, 529 patients, and 105 patients received at least 6 months, 12 months, 18 months, 24 months and 36 months of fesoterodine, respectively. The median durations of exposure to fesoterodine in the original NDA and Final Safety Update were 13.4 months and 26.3 months, respectively.

In addition, Pfizer conducted 3 new Phase 1 studies (Studies A0221004, A0221015 and A0221044) in which 106 subjects were exposed to fesoterodine. Finally, an additional 516 subjects with OAB received fesoterodine in the 12-week, Pfizer Study A0221007. The median duration of exposure in that study was 84 days.

Of all 2288 fesoterodine-treated subjects from Schwarz Pharma Phase 2/3 studies (Safety Pool S3), 961 subjects (42%) discontinued treatment prematurely. In this group, 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%).

4.3 Demographics in the Safety Update

Demographic tables were not rerun for the NDA studies conducted by Schwarz Pharma for the Final Safety Update as the Sponsor stated that these data did not change from the original NDA The demographics from the original NDA were comparable to those for the new Pfizer Study A0221007. A majority of the subjects were white females in the age group 45 – 64 years (mean age of 59.4 years).

4.4 Commonly Reported Adverse Events in the Safety Update

The following table (Table 3 of this memo - same as Table 11 from the Final Safety Update) describes the AE's seen in $\geq$ 2 % of subjects in all fesoterodine-treated subjects in Schwarz Pharma Phase 2/3 studies (Schwarz Safety Pool S3). The table shows a comparison of the reported incidences of these AE terms from the original NDA and from the Final Safety Update.

Table 3. Adverse events reported in ≥ 2 % of subjects in all fesoterodine-treated subjects in Schwarz Pharma Phase 2/3 studies (*same as Table 11 from the Final Safety Update*)

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

In this group of patients, 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 this Safety Pool.

Adverse events reported by at least 2% of fesoterodine-treated subjects in the new, 12-week, Pfizer Study A0221007 were: dry mouth (23%), constipation (5%), headache (4%), abdominal pain – inclusive of the terms abdominal pain, abdominal pain lower, abdominal pain upper and abdominal discomfort (3%), and diarrhea (2%).

In the new Phase 1 study conducted by Schwarz Pharma (Study SP857), where subjects were exposed to single doses of fesoterodine 4, 8, or 16mg or placebo, dry mouth was the most commonly reported AE. There were no SAEs or AEs leading to discontinuation in this study.

In the three new Phase 1 studies conducted by Pfizer, there were no new safety signals. In Study A0221004, a study of fesoterodine 4mg and 8mg and placebo administered once daily 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. In Study A0221044, a randomized, open-label, three-way crossover, single dose study of 4mg and 8mg dosage strengths of different formulations, the most common AE was headache. There were no SAEs or AEs leading to discontinuation in these studies and all AEs reported in the three studies were mild or moderate in intensity.

4.5 Deaths, Serious Adverse Events, and Discontinuations Due to Adverse Events in the Final Safety Update

4.5.1 Deaths

In all Schwarz studied combined, there were reports of 6 deaths. Table 4 of this memo (same as Table 13 from the Final Safety Update), is a list of these deaths, including the preferred and reported AE terms, and causality as assessed by the investigator. The medical officer's review contains narratives for these events.

Table 4. Reports of death - Schwarz Pharma Safety Pool S3

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).

Of note, the report of death of Subject 13686 was from an obituary in a local newspaper and additional attempts to contact family members for information were not successful. Therefore, causality was not assessable by the investigator. There were no deaths reported in the new Pfizer study A0221007, nor in the new Phase 1 studies.

4.5.2 Serious Adverse Events

Serious AE's were reported by 213/2288 (9%) subjects in all fesoterodine-treated patients in Phase 2/3 Schwarz Pharma studies (Safety Pool S3). This number includes an additional 55 subjects (2%) reporting SAEs after the cutoff date for the original NDA. Table 5 of this memo (same as Table 15 from the Final Safety Update) shows the incidence of all serious adverse events reported by more than 2 subjects per AE term. The table provides comparisons of SAE incidences from the original NDA and from the Final safety Update.

Table 5. Serious AE's in Phase 2/3 Schwarz Pharma Studies (Safety Pool S3) reported by at least 2 subject per AE term.

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.

In this group of patients, 1% of subjects had SAEs considered by the investigator to be at least possibly treatment related. Most SAEs assessed as at least possibly-related to treatment by the

investigator occurred in 1 subject only, with the exception of urinary retention, which was considered at least possibly related to treatment in 3 cases, and angina pectoris, diverticulitis, constipation, irritable bowel syndrome, and electrocardiogram QT corrected interval prolonged, each of which was also considered at least possibly related to treatment in 2 cases. Narratives for several of these SAEs appear in Dr. Handelsman's medical officer's review. In addition, the 2 cases described as "electrocardiogram QT corrected interval prolonged" are further discussed in Section 4.6 below.

4.5.3 Discontinuations Due to Adverse Events

In Schwarz Pharma Phase 2/3 studies (Safety Pool S3), AEs led to 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. The incidence of individual AEs leading to discontinuation in this group of patients is shown in Table 5 below (which is the same as Table 16 of the Final safety Update).

Table 5. AEs leading to discontinuation in more than 3 fesoterodine-treated subjects in the Phase 2/3 Schwarz Pharma studies (Safety Pool S3)

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.

The 8 discontinuations described as "electrocardiogram QT corrected interval prolonged" (6 from the original NDA and 2 from the Final Safety Update) are further discussed in Section 4.6 below.

4.6 Notable Issues from the Final Safety Update

4.6.1 Electrocardiographic QTc prolongation

During the Schwarz Pharma studies, including the open-label extensions, EKGs were conducted at periodic intervals and the QT interval was assessed with each EKG. The QT interval was measured without correction and with correction using Bazett's and Fridericia's correction methods. It is known that fesoterodine has an effect on increasing the heart rate, therefore, the Fridericia's method is most suitable for correction. However, during the trials, Bazett's correction was used for the discontinuation criteria. For example, the patient was to be discontinued if the QTcBazett was > 60 milliseconds above baseline or >500 millisecond on any given EKG assessment.

According to the Final Safety Update, 8 subjects (6 in the original NDA and 2 more in the Final safety Update) were discontinued based upon one or both QTc Bazett criteria. However, during the review of the Complete Response, information from the Sponsor showed that an overall total of 13 patients were discontinued based upon changes in the corrected QT. Of these, a total of 7 patients had only mild prolongation of the Bazett corrected QT interval (23-54 ms above baseline) that did not meet either per-protocol criterion for discontinuation. Two (2) patients were discontinued based upon prolongation of the Bazett corrected QT from baseline by 67 and 70 milliseconds, respectively, just slightly above the cutpoint for discontinuation. Three (3) patients were discontinued due to absolute Bazett corrected QT 500 msec (ranging from 509 to 518 msec). Finally, 1 patient was discontinued after meeting both discontinuation criteria: this 75 year old man taking 8 mg of drug for 118 days had a QTcB reported as 527 ms, up from 459 ms at baseline. In at least 2 of the 6 patients who were discontinued as a consequence of meeting at least one of the Bazett corrected QT interval discontinuation criteria, the heart rate was notably increased, implying an undercorrection when using the Bazett method.

The results of a prospectively designed and well-conducted thorough QT study using multiple doses of 4mg and 28mg revealed no evidence of QTcFridericia prolongation.

Each individual AE of QTc prolongation was reviewed by the medical officers (Dr. Suresh Kaul for the original NDA and Dr. Harry Handelsman in the Final Safety Update) and this medical team leader. Dr. Handelsman's conclusion agreed with that of the medical reviewer of the original NDA submission (Dr. Kaul) that the reported QTc prolongations were mild in intensity, somewhat exaggerated by undercorrection when using the Bazett method, frequently associated with co-morbidities and/or concomitant medications, and unlikely associated with fesoterodine.

4.6.2 Adverse Events in Patients Aged 75 years and Older

Analysis of adverse events in previous applications for antimuscurinics for overactive bladder showed that elderly patients experienced antimuscurinic adverse events more frequently than did younger patients. Therefore, the Sponsor carried out such an analysis for fesoterodine and the results again demonstrated the increased AE incidence in those aged 75 years and older. Specifically, analysis of data from the Schwarz Pharma placebo-controlled Phase 2/3 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.

5. Relevant Items from Other Disciplines

All major disciplines conducted reviews of the original NDA as well as this Complete Response. Consultative reviews were requested for several items. These are summarized herein.

5.1 Office of New Drug Quality Assessment (ONDQA)

In their final review dated September 11, 2008, Drs Rajiv Agarwal and Donna Christner of ONDQA, Division of Pre-Marketing Drug Quality Assessment concluded that:

> *"This NDA has provided sufficient CMC information to assure the identity, purity, and quality of the drug product. All facilities involved are in compliance with cGMP, and the labels have adequate information as required. Therefore, from a CMC perspective, this NDA is recommended for approval."*

Salient points from the ONDQA review included:

- Toviaz (fesoterodine fumarate), 4mg and 8gm, is an extended release tablet which is either light blue (4mg) or blue (8mg) in color, oval in shape, and film-coated.
- Fesoterodine is immediately de-esterifed to its active metabolite, a diol compound with the code name SPM 7605. SOM 7605 is also a metabolite of the approved drug tolterodine.
- The Toviaz tablet uses a [redacted] b(4)
- The tablets are manufactured by Schwarz Pharma in Germany and are tested, packaged and labeled by Schwarz Pharma in the U.S. The final recommendation from Office of Compliance for the drug product is that manufacturing and testing sites are all acceptable.
- Toviaz was originally developed with [redacted] engraved on one side of the tablets. In the Complete Response, the engraving was modified to b(4)

account for the change in ownership. For the 4mg tablet, "FS" will be engraved on one side, and for the 8mg tablet, "FT" will be engraved on one side. Comparative dissolution testing results were provided and these data supported the change in engraving.

- Five sustained release formulation were used throughout drug development. The to-be-marketed product uses Formulation F. Phase 3 studies used formulations D and E, which were successfully bridged to formulation F by in vitro dissolution data.
- The tablets are packaged as bottles and as blisters. The bottles are [redacted] and 100 cc in volume and contain [redacted] tablets, respectively. Pfizer submitted the [redacted] bottles with this Complete Response and the the DMFs in support of these containers were found to be adequate. b(4)
- The Sponsor requested 24 months shelf-life and the stability data supported this request.
- In their final review dated October 16, 2008, the Division of Medical Error Prevention and Analysis (DMEPA) had no objection to the proprietary tradename Toviaz.
- The drug substance is manufactured by Schwarz & Company in Shannon, Ireland. The final recommendation from the Office of Compliance for the Shannon site is acceptable.
- The quality of the drug substance is controlled by a host of criteria set by the manufacturer and these are deemed satisfactory.

5.2 Pharmacology/Toxicology (including Maternal Health Consult)

In their final review dated September 16, 2008, Drs Laurie McLeod-Flynn and Lynnda Reid concluded that:

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

In a supervisory Pharmacology memo dated September 16, 2008, Dr Reid concluded that:

> "*The original NDA received an approvable action pending satisfactory inspection of the manufacturing facility. Supplement N010 (the Complete Response) contains no new nonclinical data and the original recommendation that the nonclinical data supported an approval still stands.*"

In a second supervisory Pharmacology memo dated September 25, 2008, Dr. Reid commented upon labeling comments from the Maternal Health Team (MHT), received on September 19, 2008. In this memo, Dr. Reid stated:

> *"The Toviaz labeling agreed to by the Sponsor and DRUP is consistent with the other antimuscurinic drug labels. The reproductive and developmental findings for fesoterodine are similar to all other antimuscurinic products. The*

recommended changes proposed by MHT would make the Toviaz label significantly different from the other drugs of this class and may unfairly penalize it. In addition, the recommended division of the nonclinical data into summary and detailed observations is considered cumbersome and confusing in the non-PLR labeling formation.

(Therefore) We recommend that the labeling format proposed by Sponsor be retained. At the time this label is converted from non-PLR to PLR formatting, we will incorporate the recommended changes as appropriate."

The Maternal Health Team was made aware of this Pharmacology decision and they acknowledged the rationale with no objections.

There were no additional nonclinical studies in the Complete Response.

During this cycle, however, the Pharmacology team did provide input on labeling, especially to the "Carcinogenesis, Mutagenesis, Impairment of Fertility", "Pregnancy" and "Nursing Mothers" subsections of the Precautions section. During the first cycle labeling discussions, the Sponsor had accepted the Pharmacology labeling recommendations in large part. During this cycle, the Sponsor accepted all remaining labeling recommendations from the Pharmacology team. The reader is referred to my previous CDTL memo and Dr. McLeod-Flynn's primary Pharmacology review (dated December 12, 2006) for additional details of these labeling recommendations.

In regard to clinically relevant comments from the original Pharmacology review, the following items are shown again here:

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-Flynn 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)

Of note, 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.

5.3 Office of Biostatistics

Although Dr. Sobhan has not yet written a separate brief memo for this Complete Response, he did participate actively in labeling discussions during this second cycle and he did complete a review of the original NDA. There were no new statistical data for his review in this cycle.

On October 3, 2008, Dr. Sobhan and Ms. Peacock held a teleconference with Sponsor to discuss Table 2 of the Package Insert ("*Mean baseline and change from baseline to Week 12 for urge urinary incontinence episodes, number of micturitions, and volume voided per micturition.*"). This teleconference was successful in resolving all remaining minor statistical edits to this efficacy table. On October 6, 2008, the Sponsor submitted a revised Package Insert, incorporating Dr. Sobhan's recommendations. On October 7, 2008, Dr. Sobhan concurred with the final PI.

In their original review dated January 0, 2007, Drs. Sobhan and Kammerman concluded that:

> "*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.*"

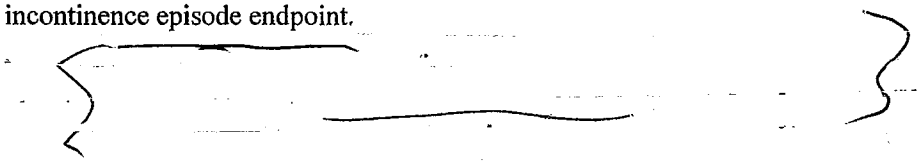
b(4)

Clinically relevant comments from the Biometrics review included:

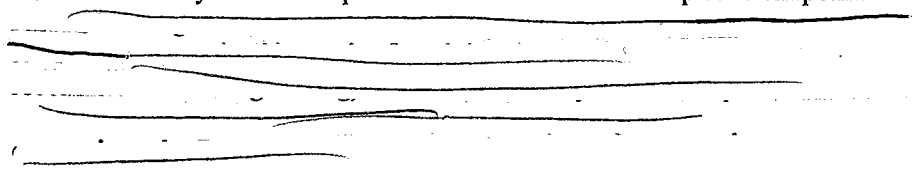
1. Biometrics performed statistical analyses with respect to the two protocol-specified co-primary endpoints for both Phase 3 studies (SP583 and SP584). The analysis supported the Sponsor's claims of efficacy for the Week 12 primary endpoint for both doses in both studies.
2. The sample size was adequate 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). Nevertheless, 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". These analyses are described in Items 4-6 that follow herein. b(4)

4. For change-from-baseline in average volume voided, Toviaz 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).
5. For change-from-baseline to Week 2 (a claim requested by the Sponsor), in Study 583, both doses of Toviaz were statistically better than placebo for the incontinence episode endpoint. b(4)



6. For change-from-baseline to Week 2 in Study 584, both doses of Toviaz were again statistically better than placebo for the incontinence episode endpoint.



Therefore, for the secondary endpoints of time-to-effect, the Sponsor agreed to

This resolution was acceptable to Dr. Sobhan and to the Clinical team. b(4)

5.4 Office of Clinical Pharmacology (OCP)

In their final review dated September 2, 2008 Drs. Kim and Tran concluded:

> *"The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds the resubmission for NDA 22-030 for fesoterodine acceptable from a Clinical Pharmacology perspective. Please see the original NDA review prepared by Dr. Doanh Tran in DFS dated December 5, 2006."*

In the re-submission, the Sponsor the results from 4 new Phase 1 studies and one study that had been previously submitted and reviewed in the original NDA. The new studies were as follows:

1) Single dose pharmacokinetics (pK) in Japanese subjects (Study SP857)
2) Multiple dose pK in Japanese males (Study A0221004)
3) Multiple dose pK in Korean subjects (Study A0221015) and
4) Single dose proportionality of 4mg and 8mg in U.S. patients (Study A0221044).

Of note, Study A0221044 also tested the bioequivalence of the to-be-marketed F formulation and another formulation called "E1". The E1 formulation was used in the Studies A0221004, A0221015, and A0221044 and may be used in future clinical studies.

In addition to these Phase 1 studies, OCP also reviewed product labeling, including a revision that emphasized the contribution of both CYP 3A4 and CYP 2D6 to the metabolic pathways of fesoterodine. Previously, the emphasis was on CYP2D6 as the major pathway with CYP3A4 described as a minor pathway.

A summary of Dr. Kim's review of the resubmission included the following clinically relevant issues:

1. Fesoterodine is rapidly de-esterified to its hydroxy metabolite, SPM 7605. SPM 7605 is also formed in vivo by metabolization of tolterodine, which is also approved for the treatment of overactive bladder (OAB).
2. Fesoterodine exposures in Japanese and Korean subjects were similar to those in Caucasian subjects.
3. In Caucasian subjects, dose proportionality between 4mg and 8mg was observed.
4. In Korean subjects, systemic exposure increased by 17-23% more than dose proportional within the 4mg to 8mg range.
5. In Japanese subjects, in one study, systemic exposure increased by 10-21% more than proportional in the 4mg - 16 mg range. However, in a different study in Japanese subjects, the systemic exposure increased 23-33% *less* than dose proportional in the 4mg to 8mg range. Dr. Kim notes that the cause of these inconsistencies is unclear.
6. The E1 and F formulations (8mg) were found to be bioequivalent.

Dr. Kim also noted that both CYP3A4 and CYP2D6 were found to be major metabolic pathways, and thus the labeling was appropriately revised by Sponsor to reflect this finding.

In his original NDA review, Dr. Tran, requested several revisions to the labeling and Sponsor agreed. These were:

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 CYP2D6 metabolizers. A table was added by Sponsor.

2. Restriction of the Toviaz dose to 4mg in patients taking concomitant potent inhibitors of CYP3A4. This restriction was added by Sponsor.

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

Additional items of note from the original OCP 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. Due to the rapid clearance, 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. Fesoterodine is well absorbed and widely distributed. Pharmacokinetics for fesoterodine 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%).

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:

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

- 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.
- 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 Toviaz 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.
- 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 Toviaz to 4mg/day in patients taking concomitant potent inhibitors of CYP3A4, such as ketoconozole.

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 Toviaz [redacted] formulation was generally "nondisintegrating", and there were no serious or life-threatening adverse events reported at doses of 16mg IR or 28mg ER. b(4)

6. There were six (6) extended-relase formulations of Toviaz during its development. 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.

5.7 Office of Surveillance and Epidemiology/Division of Medication Error Prevention and Analysis (OSE/DMEPA)

In their final consult review dated October 16, 2008, Jinhee Lee, Kellie Taylor, Denise Toyer and Carol Holquist of DMEPA (formally known as DMETS) concluded:

> *"Toviaz has some similarity to other proprietary and established drug names, but the findings of the Failure Mode and Effects Analysis (FMEA) indicates that the proposed name is not vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention and Analysis has no objections to the use of the proprietary name, Toviaz for this product."*
>
> *"The results of the Label and Labeling Risk Assessment find that the proposed container labels and labeling introduce vulnerabilites that could lead to medication errors. DMEPA's recommendations for label and labeling modifications are found in Section 5.2"*

DMEPA advised the Division that the identified labeling vulnerabilities could be addressed and mitigated prior to drug approval. There were 4 specific recommendations for revisions to the container and carton labels, and these were conveyed directly to Sponsor. They were:

1. Increase the prominence of '*Extended-release tablets*' and relocate it so it appears in conjunction with the established name. Revise the following labels and labeling accordingly:
   - Commercial Container Labels (30 tablet and 90 tablet)
   - Sample Container Labels (7 tablet, 14 tablet
   - Commercial Unit Dose Carton Labeling (100 tablet)
   - Sample Carton Labeling
   - Sample Carton Labeling
   - Sample Blister Carton Labeling
   - Sample Blister Carton Labeling

   b(4)

2. The color schemes for the 4 mg and 8 mg dosage strengths . For example, the logo includes both blue and green colors. Revise the labeling . You might consider changing the colors of the highlight bars (i.e., orange for the 4 mg, and for the 8 mg) to reduce visual similarity. Revise the following labels and labeling accordingly:
   - Commercial Container Labels (30 tablet and 90 tablet)
   - Sample Container Labels (7 tablet, 14 tablet,
   - Commercial Unit Dose Carton Labeling (100 tablet)
   - Sample Carton Labeling
   - Sample Blister Carton Labeling

   b(4)

- Sample Blister Carton Labeling

3. [redacted]

4. [redacted]

b(4)

On October 14, 2008, the Sponsor provided revised container/carton labeling and on October 15, 2008, Jinhee Lee confirmed that these 4 requests had been successfully addressed by Sponsor.

In the DMEPA consult, there was one additional comment to the Division which requires discussion here. The Sponsor had originally intended to include [redacted]

b(4)

For example, the Sponsor proposed the following:

1. [redacted]

2. [redacted]

3 [redacted]

b(4)

Both DMEPA and DDMAC (Division of Drug Marketing, Advertising and Communciation) expressed concerns about all these ancillary items. In regard to the [redacted] the sample dose carton labeling, DMEPA stated the following:

[redacted]

b(4)

The Division was in agreement with these recommendations from DMEPA and DDMAC concerning these ancillary pieces. Therefore, following a teleconference on September 29, 2008 between the Division and the Sponsor to discuss these items, the Sponsor submitted a written amendment on October 7, 2008, [redacted] b(4)

In regard to the information on the sample pack labeling, the Division requested that the Sponsor do the following:

1. Delete [redacted]
2. Delete [redacted] b(4)

In addition, the Division recommended that Sponsor also delete [redacted] from the sample dose pack carton. A final response from Sponsor to these last few DRUP requests for edits was received on October 19, 2008. The Sponsor edited the material as requested. There are no further edits recommended. b(4)

5.8. Division of Risk Management/Office of Surveillance and Epidemiology (DRISK/OSE)

The Division of Risk Management, formally the Division of Surveillance, Research, and Communication Support (DSRCS), was asked to review the Sponsor's proposed Patient Package Insert (PPI). A consult from Nancy Carothers and Jodi Duckhorn was finalized on September 10, 2008.

In their consult, DRISK made several recommendations for revising the PPI, including:

- *To inform patients that alcohol may enhance the drowsiness caused by anticholinergic agents.*
- *To inform patients that they should tell their doctors if they are taking antifungal medications since these are potent inhibitors of CYP3A4.*
- *To inform patients that the 4mg (lower dose) should be used by patients with severe kidney problems.*
- *To inform patients that use of anticholinergic agents in a hot environment can increase the risk of heat prostration.*

- *To inform patients to become familiar with the effect of anticholinergic agents on vision prior to driving or operating hazardous equipment.*
- *To inform patients that side effects should be reported to their doctors as well as to FDA.*

DRISK also made several recommendations regarding the format and order of text in the PPI. All DRISK recommendations were discussed at a PPI-specific DRUP/OSE labeling meeting. Those edits that were incorporated after the group discussion were conveyed to the Sponsor.

Subsequently, the Sponsor conveyed a revised PPI back to the Division. This document was re-reviewed by DRISK and on October 14, 2008, a final consult was completed by Nancy Carothers and Jodi Duckhorn. The consult conveyed 4 additional requests for edits to the PPI. After consideration, the Division conveyed 3 of the 4 comments to Sponsor who agreed to make those 3 recommended changes. The fourth recommendation was in regard to the specific wording of the title and placement of a single section of the PPI [redacted] b(4)
The Sponsor believes that this section should follow, not precede, the section on side effects. In addition to the rationale for the title proposed by the Sponsor (as above), the Division agrees with placement of the information after the side effects section.

5.9 Division of Drug Marketing, Advertising and Communication (DDMAC)

The Division of Drug Marketing, Advertising and Communication was consulted to provide comments from a marketing perspective on the Sponsor's proposed Package Insert (PI), Patient Package Insert (PPI) and carton labeling. The consult was completed on July 25, 2008 by Elaine Hu Cunningham and Aline Moukhtara.

In their consult, DDMAC made several recommendations for revising the PI, PPI and container labeling. Each recommendation was reviewed by the Clinical review team and also discussed at full NDA review team labeling meetings. While some of the DDMAC recommendations were instituted through labeling discussions with Sponsor, others were not. The basis for accepting some, but not all, of the DDMAC recommendations was specific information from the NDA, as well as individualized Clinical and discipline-specific judgment.

Of note, DDMAC commented upon three additional pieces: [redacted], and the sample dose pack carton. DDMAC stated that the review Division should not provide comments to Sponsor any of these 3 items, but rather the Sponsor should be encouraged to submit these to DDMAC. In response, the Division requested and the Sponsor agreed to [redacted] However, in conjunction with DMEPA, the Division did provide comments on the sample dose carton. As stated in a previous b(4)

section of this memo, the Division requested that the Sponsor revise the sample dose pack as follows:

b(4)

1. Delete
2. Delete

b(4)

A final response from Sponsor to these last few DRUP requests for edits was received on October 19, 2008 and all requested edits have been made.

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

/s/

Mark S. Hirsch
10/20/2008 10:48:28 PM
MEDICAL OFFICER

George Benson
10/21/2008 10:55:03 AM
MEDICAL OFFICER
I concur.