CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-030

SUMMARY REVIEW

Deputy Division Director Memorandum

Date	October 23, 2008
From	George S. Benson, MD
Subject	Deputy Division Director Review
NDA# Supplement#	22-030 000
Applicant	Pfizer, Inc.
Date of Submission	May 1, 2008
PDUFA Goal Date	November 2, 2008
Proprietary Name/ Established name	Toviaz/ Fesoterodine fumarate
Dosage forms/Strength	4 mg and 8 mg extended-release tablets
Proposed Indication	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency
Recommendation	Approval

Cross Divisional Team Leader	Mark Hirsch, MD
Medical Officer	Harry Handelsman, MD
Chemistry Team Leader	Donna Christner, PhD
Chemistry Reviewer	Rajiv Agarwal, PhD
Clinical Pharmacology Team Leader	Myong-Jin Kim, PhD
Clinical Pharmacology Reviewer	Hyunjin Kim, PhD
Pharmacology/toxicology Team Leader	Lynnda Reid, PhD
Pharmacology/toxicology Reviewer	Laurie McLeod-Flynn, PhD
Biometrics Team Leader	Mahboob Sobhan, PhD
Chief Regulatory Project Manager	Margaret Kober, RPh, MPA
Regulatory Project Manager	Celia Peacock, MPH, RD

1. **Introduction**
2. **Background**
3. **CMC**
4. **Nonclinical Pharmacology/Toxicology**
5. **Clinical Pharmacology**
6. **Clinical Microbiology**
7. **Efficacy/Statistics**
8. **Safety**
9. **Advisory Committee Meeting**
10. **Pediatrics**
11. **Other Relevant Regulatory Issues**
12. **Labeling**
13. **Decision/Action/Risk Benefit Assessment**

1. Introduction

Anticholinergic drugs (muscarinic antagonists) have been a mainstay of overactive bladder therapy for decades. Fesoterodine fumarate is a muscarinic receptor antagonist agent which is proposed for the indication "treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency" in NDA 22-030. Currently approved oral agents in this drug class for the overactive bladder indication include oxybutynin (Ditropan), tolterodine (Detrol), solifenacin (Vesicare), darifenacin (Enablex), and trospium (Sanctura). The mechanism of action of these drugs is blockade of cholinergic (muscarinic) receptors in the bladder detrusor muscle and, therefore, inhibition of bladder contractility. Fesoterodine is rapidly and extensively metabolized to an active metabolite (5-hydroxytolterodine) which is also the major active metabolite of the approved drug tolterodine (Detrol).

2. Background

NDA 22-030 was originally submitted on March 17, 2006, and received an "approvable" action on January 25, 2007. The single major deficiency identified in the "approvable" letter was:

"Pre-approval Inspection (PAI) of your active pharmaceutical ingredient (API) manufacturing facility, Schwarz Pharma Ltd., located in Shannon, Ireland, could not be conducted because the site has not been available for PAI during this review cycle, as stated in your letter, dated July 20, 2006. Satisfactory inspection of your API manufacturing facility, Schwarz Pharma Ltd., located in Shannon, Ireland, is required before this application may be approved."

In addition to the manufacturing facility inspection, "labeling remains unresolved."

The sponsor submitted a complete response to the "approvable" action on May 1, 2008. The safety update in the complete response included updated safety data from three long-

term open-label extension studies, an ongoing 12-week, open label study, and five new Phase 1 studies.

3. CMC

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

The drug substance manufacturing site in Shannon, Ireland, received an "acceptable" inspection (June, 17, 2008). The lack of this facility being available for inspection was the primary basis for the "approvable" action taken during the first review cycle.

The requested shelf life of 24 months for the 4 and 8 mg tablets packaged in bottles with desiccant and in aluminum/aluminum blister was granted.

4. Nonclinical Pharmacology/Toxicology

No new non-clinical data were submitted in the complete response. All required nonclinical studies were submitted in the original NDA submission and included subchronic toxicology studies in mice, rats, and dogs, 6 and 9 month chronic toxicology studies in mice and dogs, respectively, reproductive and developmental studies in mice and rabbits, full battery of genotoxicity studies, 2-year carcinogenicity studies in mice and rats, evaluation of skin and eye irritation potential, and in vitro assessment of phototoxicity.

The nonclinical reviewers believe that the "non-clinical data support an approval."

5. Clinical Pharmacology

The clinical pharmacology review stated that "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."

Fesoterodine is a new molecular entity but its metabolite SPM 7605 is the same as the active metabolite of the approved drug tolterodine. Fesoterodine undergoes rapid deesterification to its hydroxy metabolite, SPM 7605. Following oral administration, the parent compound fesoterodine can not be detected in plasma and fesoterodine's pharmacokinetics (PK) is described by its active metabolite SPM 7605. CYP2D6 and CYP3A4 are the two major metabolic enzymes responsible for the metabolism of SPM 7605.

Important clinical pharmacology conclusions and labeling recommendations include:

The results of a "thorough QT study" (SP686) demonstrated that fesoterodine 4 and 28 mg/day for 3 days did not appear to have a significant effect on the QTc interval. Fesoterodine causes a dose dependent increase in heart rate.

Sex, age, and race have no significant effect on the PK of fesoterodine.

Hepatic impairment: Moderate liver impairment increases the C_{max} and AUC of SPM 7605 by 1.4 and 2.1 fold, respectively. The clinical pharmacology reviewer believes that no dose adjustment is needed in patients with moderate hepatic impairment. The effect of severe hepatic impairment has not been evaluated. Fesoterodine is not recommended for use in patients with severe hepatic impairment because of the potential for increased drug exposure in this group of patients.

Renal impairment: In patients with mild renal impairment, C_{max} and AUC were 1.3 and 1.6 fold higher, respectively, than in patients with normal renal function. In patients with moderate renal impairment, C_{max} and AUC values were 1.5 and 1.8 fold higher than in patients with normal renal function. In subjects with severe renal impairment, C_{max} and AUC values were 2.0 and 2.3 fold higher than in subjects with normal renal function. The clinical pharmacology reviewer recommends no dose adjustment in patients with mild and moderate renal impairment and agrees with the sponsor's proposal to limit patients with severe renal impairment to doses no greater than 4 mg/day. I agree.

CYP2D6 poor metabolizers: CYP2D6 PMs have C_{max} and AUC values that are approximately 2-fold higher than CYP2D6 EMs. In limited data from phase 3 trial SP584, CYP2D6 PMs did not have higher baseline corrected heart rates than EMs. Although side effects of dry mouth and constipation were higher in the 8 mg dose group compared to the 4 mg dose group, no significant safety problems were encountered in both the CYP2D6 EM and PM patient populations. The safety risk of this two-fold increase in exposure appears to be low. The clinical pharmacology reviewer does not recommend a dose adjustment in CYP2D6 PMs.

Concomitant food intake causes a mean increase in C_{max} of 19-30% and AUC by 18-19%. These small increases are not thought to be clinically significant.

CYP3A4 inhibition: The concomitant administration of fesoterodine and ketoconazole increased SPM 7605 Cmax by 2.0-2.1 fold and AUC by 2.3-2.5 fold. Administration of fesoterodine to patients who are CYP2D6 PMs who are also taking ketoconazole 200 mg twice daily resulted in increases of 5.69 and 4.48 fold in AUC and C_{max} of SPM 7605, respectively, compared with CYP2D6 EMs with no concomitant CYP3A4 inhibitor. The clinical pharmacology reviewer recommended that the fesoterodine dose be restricted to no more than 4 mg/day when given to a patient taking a strong CYP3A4 inhibitor.

Concomitant administration of fesoterodine with an oral contraceptive containing ethinylestradiol and levonorgestrel did not significantly affect the plasma levels of ethinylestradiol and levonorgestrel.

I agree with the clinical pharmacology reviewer's labeling recommendations.

6. Clinical Microbiology

There are no outstanding issues and the "microbiological attributes" are considered "adequate."

7. Efficacy/Statistics

To support efficacy for the overactive bladder indication, the sponsor reported the results of two phase 3 trials (Trial SP583 conducted in Europe and Trial SP584 conducted in the United States). Both trials were randomized, double-blind, placebo-controlled, fixed-dose, parallel arm studies comparing fesoterodine 4mg/day, fesoterodine 8 mg/day, and placebo for a treatment interval of 12 weeks in a well-defined population of patients with overactive bladder.

Entry criteria included:

- Greater than 18 years of age
- Minimum 6-month history of symptoms of OAB or urge incontinence
- Completion of a voiding diary for 3 consecutive days during the week prior to randomization
- Minimum of 3 urge incontinence episodes and 8 micturitions/24hrs during the above diary period

Primary endpoints:

Primary Endpoint:

The primary endpoint for the two phase 3 trials (SP-583 and SP-584) is change in number of micturitions (frequency) per 24 hours (from baseline to the end of 12 weeks of treatment).

Co-Primary Endpoint:

Change in number of urge incontinence episodes per 24 hours (from baseline to the end of 12 weeks of treatment).

The two primary endpoints are currently standard primary endpoints for overactive bladder trials.

In study SP-583 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 an active comparator (tolterodine 4mg/day). Most patients (>80% in any treatment group) completed the full 12 weeks of treatment. Most of patients (81%) were females with a mean age of 57 years and an overall age range of 19 to 86 years.

In study SP-584 a total of 836 patients were randomized and 832 patients treated: 266 with placebo, 267 with fesoterodine 4mg/day and 267 patients with fesoterodine 8mg/day. Most patients (>80% in any treatment group) completed the full 12 weeks of treatment. The majority (76%) of patients were females, with a mean age of 59 years and an overall age range of 21 to 91 years. A total of 9% of patients were poor metabolizers for CYP2D6.

The results for the two co-primary endpoints in the two phase 3 studies (SP-583 and SP-584) are shown in Tables 1 and 2.

Table 1. 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	-1.20(3.3)	-2.06(2.7)	-2.27(2.4)	-1.0(2.7)	-1.77(3.1)	-2.42(2.8)
P-value for change from baseline vs. placebo		P=0.001	P<0.001		P=0.002	P<0.001

Mean (SD) – Sample size reflects number of patients at baseline
Analysis reflects baseline to endpoint using LOCF.

Only those patients who experienced urge incontinence 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, fesoterodine 4 mg/day and fesoterodine 8 mg/day groups, respectively. In Study 2, the number of these patients was 205, 228, and 218, respectively.

Table 2. 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	-1.02(3.0)	-1.74(2.7)	-1.94(3.1)	-1.02(3.4)	-1.86(3.6)	-1.94(3.0)
P-value for change from baseline vs. placebo		P<0.001	P<0.001		P=0.032	P<0.001

Mean (SD) – Sample size reflects number of patients at baseline
Analysis reflects baseline to endpoint using LOCF.

Statistical review:

The statistician's review of the efficacy data 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 fesoterodine (4 and 8 mg) significantly ($p<.05$) reduced the average number of micturitions and urge incontinence episodes."

The primary medical officer during the first cycle review concluded that "fesoterodine results are similar in magnitude of improvement for change in the number of the micturitions per 24 hours, urge incontinence episodes per 24 hours and volume voided regardless of patient's age, gender or race."

Efficacy summary:

The results from both randomized, placebo-controlled primary phase 3 studies demonstrated that fesoterodine 4 mg and 8 mg administered once daily for 12 weeks improved the primary efficacy variables compared to placebo. The results were dose-responsive and statistically significant. The medical reviewers believe that the recommended dosing regimen should be a starting dose of 4 mg in all patients. If tolerability allows, and efficacy necessitates, patients may be titrated up to an 8 mg/day dose. Despite the lack of a placebo-controlled, dose-titration efficacy study, the medical reviewers support the recommended dose-titration scheme because the 4 mg dose is efficacious and safety will be enhanced. I support this recommendation. No adequately designed and controlled studies have been performed to compare the efficacy of fesoterodine to other approved anticholinergic agents for the treatment of overactive bladder.

8. **Safety**

In the original NDA submission, safety data were drawn from total of 2288 patients with overactive bladder (OAB) who received fesoterodine in phase 2 and 3 trials during the drug development program. This includes 858 (38%) patients exposed to fesoterodine for >6 months, 570 (25%) patients exposed for >12 months and 162 (7%) patients exposed for >18 months. There were also 489 patients who received fesoterodine during Phase 1 trials.

The safety update submitted in the complete response to approvable (May 1, 2008) contained updated safety data from three long-term open-label extension studies, an ongoing 12-week, open label study, and five new Phase 1 studies. These updated additional safety data include >500 patients exposed to fesoterodine for at least 2 years and >100 patients exposed for at least 3 years.

Deaths occurring in placebo and active controlled phase 3 studies:

Six deaths were reported from all placebo and active controlled studies. None of the deaths was judged by the investigators to be related to the use of fesoterodine.

Of the six patients who died during the drug program development, one patient (#10672) in study SP582 died from cerebrovascular accident, the second patient (#10527) in study SP 583 died from myocardial infarction, the third patient (#10943) in study SP738 died from to metastastases to the liver, the fourth patient (#11184) in study SP738 died due to "sudden death," the fifth patient (#10618) died several months after completing study SP 583 due to unknown causes, and the sixth patient died of "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 to the trial medication.

The primary medical officer reviewed the narratives of these six cases and agreed with the investigators that none of the six deaths was related to the use of fesoterodine.

Serious adverse events (SAE's):

In the original NDA submission, SAE's were reported in patients treated with placebo, fesoterodine 4mg, 8mg, 12mg/day; or the active comparator tolterodine 4mg/day in 2%, 4%, 3%, 6%, and 2% of patients in these treatment groups. The primary medical officer concluded that Serious AE's in all treatment groups occurred across multiple body systems with no obvious trends. During long-term open-label treatment, SAE's occurred in 9% of patients. Serious AEs reported by more than 2 patients during open-label treatment were myocardial infarction in 4 (<1%) patients, and breast cancer, bronchitis, knee arthroplasty, and cholecystectomy which were each reported by 3 patients.

The narratives non-fatal SAE's from phase 3 trials SP-583 and SP-584 are summarized in Tables 3 and 4.

Table 3: Non-fatal SAE's In SP 583:

SP583 Patient #	Age/ Gender	SAE	Dose/Day	Intensity	Causality
10048	72/M	Femoral neck fracture	4mg	Moderate	Not related
10055	49/F	Asthma	4mg	Moderate	Not related
10125	54/F	Hip arthroplasty	8mg	Severe	Not related
10258	72/M	QT prolongation on ECG	8mg	Mild	Possible
10288	70/M	Angina Pectoris	0mg	Severe	Possible
10339	72/F	Unstable Angina	8mg	Severe	Unlikely
10472	78/F	Tibia fracture	0mg	Severe	Not related
10480	58/F	Heart failure	4mg	moderate	Not related
10527	70/F	Bronchitis MI	8mg 0mg	Severe Severe	Not related Not related
10535	60/F	QTc prolongation on ECG	8mg	Mild	Unlikely
10618	82/F	Fracture Patella Depression Death	0mg 0mg 0mg	Severe Severe Not assessed	Not related Not related Not related
10700	53/F	Basedow's disease	4mg	Mild	Not related
10715	30/F	Salpingitis	4mg	Moderate	Not related
10766	52/F	Gastroentritis	4mg	Severe	Possible
10806	58/F	Dyspepsia	4mg	Moderate	Unlikely
10874	63/M	Pneumonia	8mg	Severe	Unlikely
10885	50/F	Eczema	0mg	Mild	Not related
11034	54F	Depression	4mg	Moderate	Not related
11037	66/M	Cholithiasis	0g	Severe	Unlikely
11048	75/F	Arthalgia Joint Dislocation	0mg 0mg	Moderate Moderate	Not related Not related
11126	72/F	Breast Surgery	8mg	Mild	Not related
11159	25/F	Abdominal Pain	4mg	Moderate	Not related
11185	68/F	Sciatica	8mg	Moderate	Unlikely
11328	48/F	Chest Pain	4mg	Mild	Possible
11348	52/F	Endometrial hypertrophy	8mg	Mild	Not related
11410	54/F	Abnormal Labs	0mg	Mild	Not related
11446	47/F	Implant complication	4mg	Moderate	Not related

Table 4: Non-fatal SAE's In SP 584:

SP584 Patient #	Age/ Gender	SAE	Dose/Day	Intensity	Causality
13017	47/F	Appendicitis	4mg	Moderate	Not related
13066	58/F	Sinusitis	8mg	Severe	Not related
13316	61/F	Pneumonia	0mg	Moderate	Not related
13551	61/F	Chest Pain	4mg	Severe	Not related
13809	46/F	Spinal decompression	4mg	Moderate	Not related
14131	62/M	Malignant Melanoma	4mg	Severe	Not related
14190	67/F	Abnormal LFT's	0mg	Severe	Not related
14207	64/F	Brain neoplasm	8mg	Mild	Unlikely
14330	42/F	Viral gastroentitis	8mg	Severe	Not related
14505	66/F	Knee arthroplasty	8mg	Moderate	Not related
14583	68/F	Ankle fracture	4mg	Moderate	Unlikely
14703	49/F	Colitis	4mg	Severe	Not related
14716	47/F	Rotator cuff repair	8mg	Severe	Not related
14776	62/M	Thoracotomy	4mg	Severe	Not related
14861	58/F	Cataract	4mg	Severe	Not related

In addition to the above SAE's, a case of pancreatitis was reported in a 72-year-old woman who received fesoterodine for 16 months during SP-739 trial (an open-label extension of trial SP584). The patient had a history of cholecystectomy and other co-morbid medical conditions and was also on other concurrent medications. The event was determined by the investigator as unlikely related to fesoterodine.

The medical reviewers concluded that the serious adverse events reported in the phase 3 trials did not raise significant safety concerns with fesoterodine use and I agree.

Common Adverse Events:

Table 5 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 fesoterodine 4 or 8 mg once daily for up to 12 weeks.

Table 5 . 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, fesoterodine 4 mg/day, and fesoterodine 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, fesoterodine 4 mg/day and fesoterodine 8 mg/day groups respectively. The most common adverse event leading to discontinuation was dry mouth. 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 5 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.

A modestly increased incidence of anticholinergic adverse effects in patients aged 75 years and greater compared to patients younger than 75 years was noted and described in the medical team leader's review. Of 1120 patients who received fesoterodine 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. The incidence of commonly reported anticholinergic adverse events (constipation, urinary tract infection and dizziness), however, was higher in patients 75 years of age and older as compared to younger patients. This information has been added to the label. 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.

Summary of Clinical Laboratory Findings:

According to the medical officer's review, overall, 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 that there was no clinically relevant pattern of laboratory abnormalities reported as AE's that resulted in withdrawal. Likewise, while there were individual cases that exceeded the normal range for individual laboratory parameters, there were no trends in occurrence of markedly abnormal laboratory findings.

There were isolated cases of mild to moderate elevations in AST, ALT, and GGT. Similar proportions of patients in all treatment groups met the 2.5 X ULN criterion. No fesoterodine-treated patient had an AST/ALT elevation above 2.5-3.0 X ULN and a bilirubin above ULN.

Review of the new safety data included in the complete response submission shows it to be consistent with previously reported data in the original NDA and the original 120 day safety update. (An overview of the final safety update can be found on pages 8 to 15 of the Cross Divisional Team Leader's review). No new risks or safety issues were identified by the medical officer in the review of the complete response submission.

Safety summary:

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

- The reported adverse clinical events for fesoterodine 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 28 mg once a day.
- No significant hepatotoxicity was reported in any trials of fesoterodine, although there were a few patients with mild increases 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).

9. **Advisory Committee Meeting**

Fesoterodine is the sixth orally administered anticholinergic drug to be approved for the indication "treatment of overactive bladder." Although fesoterodine is a new molecular entity, the drug is rapidly metabolized to the active metabolite 5-hydroxytolterodine which is also the major metabolite of the approved drug tolterodine. Although no "head to head" adequately controlled trials have compared fesoterodine to other approved anticholinergic drugs, the efficacy appears to be roughly comparable and no new safety concerns have been identified. No advisory committee was convened.

10. **Pediatrics**

The Pediatric Review Committee (PeRC) agreed with the partial waiver for patients less than 5 years of age and deferral of patients 6 to / years, 11 months of age. The PeRC recommended that the Division add the dates for the protocol submission and the date the studies are due to the Approval letter. Overall, PeRC agreed with the deferral and overall pediatric plan. b(4)

11. **Other Relevant Regulatory Issues**

a. Division of Scientific Investigations (DSI):

DSI concluded that inspection of 3 of the 4 clinical sites did not reveal any significant regulatory violations. Overall, "the data appear acceptable in support of the respective indication." The inspection of the fourth site revealed deficiencies with diary entries for seven of 17 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 DRUP clinical review team and the 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.

b. Division of Medication Error Prevention and Analysis (DMEPA):

DMEPA "has no objections to the use of the proprietary name Toviaz for this product."

c. Office of Surveillance and Epidemiology (OSE):

A pre-approval safety meeting with representation from OSE was held. The safety data submitted in the original NDA and the complete response submission were discussed. Specifically, data relating to central nervous system, cardiac (including QT prolongation), hepatic, and skin (rash) events were reviewed. The overall safety profile of fesoterodine, as well as the safety profiles of other approved anticholinergic agents, were discussed. Labeling was also reviewed.

No new safety concerns were identified and the labeling appears adequate for safe use of the drug. No post-marketing commitments were thought to be necessary. No specific safety data were identified which would require other than routine post-approval surveillance.

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

DDMAC was consulted to comment on product labeling from a marketing and advertising perspective. All DDMAC comments were considered and acted upon as deemed appropriate by DRUP.

e. Financial disclosure:

The financial disclosure information submitted in the original NDA submission was reviewed and found to be acceptable. No inappropriate financial arrangements relating to study investigators were identified.

12. **Labeling**

The label and patient package insert have been agreed upon with the sponsor.

13. **Decision/Action/Risk Benefit Assessment**

I agree with the recommendations of the cross divisional team leader, primary medical officer, clinical pharmacology reviewer, pharmacology/toxicology reviewer, CMC reviewer, and statistical reviewer that NDA 22-030 (fesoterodine for the treatment of overactive bladder) be approved.

Efficacy using accepted endpoints (incontinence episodes and urinary frequency) was demonstrated in two adequate, controlled phase 3 studies. Fesoterodine is an anticholinergic agent whose safety profile appears similar to other approved anticholinergic drugs, although no well designed or controlled comparative studies have been performed. No new safety concerns have been identified. Adverse events appear to be related to the known pharmacology of anticholinergic drugs.

No post-marketing studies are required.

Labeling negotiations have been satisfactorily concluded.

There are no outstanding issues related to this NDA, and I recommend approval.

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

/s/

George Benson
10/23/2008 10:48:04 AM
MEDICAL OFFICER