# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**22-030**

# SUMMARY REVIEW

## Deputy Division Director Memorandum

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| Date | October 23, 2008 |
| From | George S. Benson, MD |
| Subject | Deputy Division Director Review |
| NDA#<br>Supplement# | 22-030<br>000 |
| Applicant | Pfizer, Inc. |
| Date of Submission | May 1, 2008 |
| PDUFA Goal Date | November 2, 2008 |
| Proprietary Name/<br>Established name | Toviaz/<br>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 |

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## 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.

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