CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-030

OFFICE DIRECTOR MEMO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 31, 2008

FROM: Julie Beitz, MD

SUBJECT: Office Director Memo

TO: NDA 22-030 Toviaz (fesoterodine fumarate) extended-release tablets; Pfizer, Inc.

Summary
Fesoterodine fumarate is a muscarinic receptor antagonist that inhibits detrusor contractions and enhances bladder capacity. This memo documents my concurrence with the Division of Reproductive and Urologic Product's (DRUP's) decision that fesoterodine fumarate for the treatment of adults with overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency be approved. The recommended starting dose is 4 mg once daily. Based upon individual response and tolerability, the dose may be increased to 8 mg once daily. The daily dose should not exceed 4 mg in patients with severe renal insufficiency or in patients taking potent CYP3A4 inhibitors. Fesoterodine fumarate is not recommended for use in patients with severe hepatic impairment.

Regulatory History
NDA 22-030 was originally submitted by Schwarz Pharma Inc. on March 17, 2006, and received on March 27, 2006. The sponsor's API manufacturing facility in Shannon, Ireland, was not ready for FDA's pre-approval inspection during the initial review cycle. On January 25, 2007, an approvable letter was issued stipulating that a satisfactory inspection of this site would be needed prior to approval and requesting that an updated summary of safety be submitted with the sponsor's future response. On May 1, 2007, Schwarz Pharma Inc. submitted a complete response to the approvable letter. On August 1, 2007, ownership of this NDA was transferred from Schwarz Pharma, Inc. to Pfizer, Inc. During this review cycle, inspection of the Ireland manufacturing site was completed and it was found to be acceptable.

This application was not referred to an FDA advisory committee because fesoterodine fumarate is a member of the anti-muscarinic class of products used to treat overactive bladder, including previously approved products. Fesoterodine fumarate did not pose unique concerns beyond those applicable to other members of this class.

Efficacy
The efficacy of fesoterodine fumarate is supported by two 12-week randomized, placebo-controlled phase 3 trials that enrolled adult patients with overactive bladder (with a combined total of 554 patients on fesoterodine fumarate 4 mg daily, 566 on fesoterodine fumarate 8 mg daily, and 554 on placebo). Patients were required to have overactive bladder symptoms for at least 6 months prior to study entry. The majority of patients were female (79%) with a mean age of 58 years. Both trials showed a statistically significant reduction from baseline to endpoint (Week 12) in the number of urge urinary incontinence episodes per 24 hours for the 4 and 8 mg fesoterodine fumarate doses compared to placebo treatment. Both trials also showed a statistically significant reduction from baseline to endpoint (Week 12) in the number of micturitions per 24 hours for the 4 and 8 mg fesoterodine fumarate doses compared to placebo treatment. A reduction compared to placebo in the number of incontinence episodes was seen as early as 2 weeks following the start of fesoterodine fumarate treatment.

For the secondary endpoint of voided volume per micturition, one of the phase 3 trials showed significant increases for both daily doses of fesoterodine fumarate compared to placebo treatment. In the second trial,

significant improvement in voided volume was observed for the 8 mg daily dose but not for the 4 mg daily dose.

Safety

A total of 2288 patients with overactive bladder received fesoterodine fumarate in phase 2 and 3 clinical trials. Of these, 782, 785, and 222 patients received fesoterodine fumarate doses of 4 mg, 8 mg, or 12 mg respectively, in Phase 2 and 3 trials with treatment periods of 8 to 12 weeks. Approximately 80% of these patients had > 10 weeks of exposure in these trials. Longer exposures to fesoterodine fumarate were observed in 857 patients for ≥ 6 months, in 701 patients for ≥ 12 months, in 529 patients for ≥ 24 months, and in 105 patients for ≥ 36 months. The safety profile for fesoterodine fumarate is consistent with that of other anti-muscarinics marketed for the treatment of overactive bladder; in fact, fesoterodine fumarate produces the same active metabolite as does tolterodine, a drug already marketed for this use. The most common adverse events reported were dry mouth, constipation and urinary retention. These events were generally mild or moderate in intensity. The incidence of dry mouth was highest in those taking 8 mg daily (35%) as compared to 4 mg daily (19%) or placebo treatment (7%). As with other anti-muscarinics, use of fesoterodine fumarate is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma.

A randomized, double-blind, placebo- and moxifloxacin-controlled study involving 261 subjects and designed to evaluate the risk of QT prolongation at therapeutic and supratherapeutic doses of fesoterodine fumarate (4 and 28 mg daily doses) did not demonstrate abnormalities in cardiac repolarization related to fesoterodine fumarate use.

Fesoterodine fumarate is associated with an increase in heart rate. In the phase 3 trials, the mean increase in heart rate compared to placebo was 3-4 beats/minute in patients treated with 4 mg daily and 3-5 beats/minute in patients treated with 8 mg daily.

No evidence of drug-related carcinogenicity was found in 24-month studies of oral administration to mice and rats. Fesoterodine fumarate was not mutagenic or genotoxic *in vitro* or *in vivo*.

Fesoterodine fumarate produced no dose-related teratogenic effects in mice and rabbits. Following oral doses 6-27 times the maximum human recommended dose (MHRD), female mice demonstrated increased resorptions and decreased live fetuses; fetuses with cleft palate were also noted at an incidence within the background range. Following oral administration to female rabbits, incomplete ossification of the sternebrae (retardation of bone development) was noted in fetuses. There have been no adequate and well-controlled studies of fesoterodine fumarate conducted in pregnant women. DRUP has proposed, and I concur, with a Pregnancy Category C, i.e., that this product should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pharmacokinetic Considerations

Following oral administration, fesoterodine fumarate is rapidly and extensively hydrolyzed to its active metabolite, 5-hydroxymethyl tolterodine, which is responsible for the anti-muscarinic activity of fesoterodine fumarate. The active metabolite is further metabolized in the liver with involvement of CYP2D6 and CYP3A4. Exposure to the active metabolite is doubled in poor metabolizers of CYP2D6 as compared to extensive metabolizers. Poor metabolizers of CYP2D6 were also more likely than extensive metabolizers to experience anti-muscarinic adverse events (e.g., dry mouth), particularly at the 8 mg daily dose, however, no dosing adjustments are recommended based solely on intrinsic CYP2D6 metabolizer status. Co-administration of ketoconazole, a potent inhibitor of CYP3A4, with fesoterodine fumarate also increased exposure to the active metabolite two-fold; dry mouth occurred in up to 43% of patients co-administered fesoterodine fumarate 8 mg daily and CYP3A4 inhibitors. Exposure was calculated as being nearly 6-fold higher in CYP2D6 poor metabolizers taking ketoconazole as compared to CYP2D6 extensive metabolizers not taking ketoconazole. Therefore, doses of fesoterodine fumarate greater than 4 mg are not recommended in patients taking potent CYP3A4 inhibitors.

In patients with moderate (Child-Pugh B) hepatic impairment, C_{max} and AUC of the active metabolite are 1.4- and 2.1-fold higher respectively, as compared to healthy subjects. No dose adjustment is

recommended for patients with mild to moderate hepatic insufficiency. Patients with severe hepatic impairment have not been studied; fesoterodine fumarate is not recommended for use in these patients.

In patients with mild to moderate renal insufficiency (creatinine clearance of 30-80 mL/min), C_{max} and AUC of the active metabolite are 1.5- and 1.8-fold higher respectively, as compared to healthy subjects. In patients with severe renal insufficiency (creatinine clearance of < 30 mL/min), C_{max} and AUC are 2.0- and 2.3-fold higher, respectively. No dose adjustment is recommended for patients with mild or moderate renal insufficiency. Doses of fesoterodine fumarate greater than 4 mg are not recommended in patients with severe renal insufficiency.

Tradename Review

The tradename "Toviaz" was submitted for review on April 1, 2008 and found to be acceptable. The previously submitted proposed tradename '[redacted] was also found acceptable. b(4)

Postmarket Studies

The pediatric study requirement under PREA will be waived for ages 0 months to 5 years, 11 months, because necessary studies are impossible or highly impracticable. This is because study endpoints are difficult to evaluate in this age group.

Submission of the pediatric study for ages 6 to 16 years, 11 months, is deferred because the product is ready for approval for use in adults and the pediatric study has not been completed. The deferred study will evaluate fesoterodine fumarate for the treatment of overactive bladder in the subgroup of pediatric patients with neurologic disease.

No postmarket studies or clinical trials will be required under Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007.

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Julie Beitz, MD
Director,
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/s/

Julie Beitz
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DIRECTOR

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