Medical Officer's Review of NDA

Fesoterodine [redacted] b(4)

NDA 22-030

Date of Submission:	**March 27, 2006**
NDA Goal Date:	**January 27, 2007**
Target Action Date:	**January 26, 2007**
Sponsor:	**Schwarz Biosciences, Inc.**

Drug Name:	
Proposed Trade Name:	[redacted] b(4)
Proposed Drug Name:	**Fesoterodine**
Pharmacologic Category:	**Anti-Cholinergic (Muscarinic Receptor Antagonist)**
Phase 3 Studies Reviewed:	**SP584, SP583 & SP686**

Indication:	**Treatment of Overactive Bladder (OAB)**
Doses Used:	**4mg & 8mg once a day**
Route of Administration	**Oral**

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I. Executive Summary

I.1. Recommendations

In the opinion of this reviewer, from a clinical perspective, fesoterodine 4mg and 8mg tablets taken once daily **should be approved** for the Sponsor's proposed indication "**treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and urinary frequency**" in adult men and women.

The evidence presented in the submission of this NDA is adequate in support of the effectiveness of fesoterodine. The adverse events profile of fesoterodine appears to be similar to other approved antimuscarinic drugs in its class. The safety evaluation exceeds the ICH guidance criteria for the number of patients exposed to fesoterodine and for the duration of exposure. Thorough QT safety assessment from study **SP686** showed no signal of an effect at the clinical dose of 4mg and supra-therapeutic dose of 28mg once a day on ventricular repolarization or cardiac conduction.

I.2. Summary of Clinical Findings

I.2.A. Brief Overview of Clinical Program

Fesoterodine is a new chemical entity that belongs to the class of antimuscarinic agents. Fesoterodine has been developed as a sustained release (4mg & 8mg), once daily formulation for the proposed indication of treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

Fesoterodine is a non-selective muscarinic receptor antagonist. Following oral administration, fesoterodine is completely absorbed and de-esterified in vivo to the active metabolite **SPM 7605**. Maximum plasma levels of **SPM 7605** are achieved approximately 5 hours after administration of fesoterodine SR. Steady state is reached after 3 days and the major pathway for metabolism is via **CYP2D6**. Terminal half life of oral fesoterodine is approximately 7 hours. Hepatic metabolism and renal excretion contribute significantly to the elimination of **SPM 7605**. Approximately 70% of orally administered dose is recovered in urine as metabolite(s) and 7% is recovered in the feces. **SPM 7605** is distributed widely in the body, as shown by the apparent volume of distribution of 519L after IV administration of fesoterodine. The metabolites of fesoterodine other than **SPM 7605** have low or no in vitro binding to muscarinic acetylcholine receptors. In poor metabolizers of CYP2D6, exposure to SPM 7605 was approximately doubled. Inhibition of CYP3A4 by ketoconazole resulted in an approximately 2-fold increase in exposure to SPM7605. Induction of CYP3A4 by rifampin resulted in approximately 4 fold reduction in exposure to SPM 7605. No other notable drug–drug interactions have been reported.

A total of 17 Phase 1 trials in healthy patients, and three Phase 2 trials and two Phase 3 trials in patients with OAB syndrome have been conducted during the fesoterodine development program. Approximately 489 healthy subjects have received fesoterodine in Phase 1 trials and approximately 2288 patients with OAB have received fesoterodine in Phase 2 and 3 trials. In all these trials fesoterodine has been safe and well tolerated.

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During the EOP2 meeting in June 2003, the sponsor was advised to conduct two, 12-week, placebo-controlled trials with micturition frequency, urge incontinence episodes and the volume voided as the key endpoints. The sponsor was also advised to conduct a thorough QT trial preferably in the target population and to perform genotyping for CYP 2D6 metabolizer status in at least one Phase 3 trial.

At the pre-NDA meeting in July 2005, the Division concurred that the sponsor had conducted the requested Phase 3 and thorough QT studies and also concurred with the sponsor's request for partial waiver/deferral for pediatric patients.

I.2.B. Efficacy

The co-primary endpoints and the key secondary endpoint for the pivotal studies are appropriate and clinically meaningful. The study results provide substantial evidence in support of effectiveness of fesoterodine 4mg and 8mg taken orally once daily for the treatment of patients 18 years and older with symptoms of overactive bladder (OAB).

The conclusions from the clinical efficacy review were as follows:

- Fesoterodine showed a statistically significant and clinically meaningful improvement in decreasing the number of micturitions during an average 24 hour period when compared to placebo over a treatment period of 12 weeks in both SP583 and SP584 trials.

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- For incontinence episode frequency, there was a clinically meaningful decrease shown in both pivotal studies and the improvements were statistically significant when compared to placebo. The improvement in incontinence episode frequency was statistically significant as early as 2 weeks after the start of treatment in both studies for the 4mg dose (the starting dose).

- For volume voided, fesoterodine increased the average volume per void in both studies. The increase was statistically significant at the $p < 0.001$ level for both fesoterodine 4mg and 8mg/day in study SP583, but only statistically significant in the 8mg dose group in study SP584.

- Fesoterodine also demonstrated a significant improvement in other clinical secondary endpoints in both Phase 3 studies.

- The magnitude of the fesoterodine treatment effect was consistent across different age groups, race and gender.

I.2.C. Safety

Safety data is primarily drawn from a total of 2288 patients with OAB who received fesoterodine SR in phase 2 and 3 trials during the drug development program. This includes 858 (38%) patients exposed to fesoterodine for >6months, 570 (25%) patients

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exposed for >12 months and 162 (7%) patients exposed for >18months. There were also 489 patients that received fesoterodine during Phase 1 trials.

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

Important safety-related findings from the clinical review were:

- Dry mouth, constipation, abdominal pain, headache, urinary retention, dry eyes and urinary tract infection were the most frequently reported adverse events that occurred in the two pivotal studies SP583 and SP584.
- Most reported clinical adverse events were mild to moderate in severity and resolved without significant medical intervention.
- The anti-muscarinic adverse events seen 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. This review took into consideration cases of chest pain, angina, MI, heart failure, QTc prolongation on ECG, pneumonia, bone fractures, spinal decompression, salpingitis, appendicitis, skin disorders and abnormal LFT's. All these adverse events were mild to moderate in intensity and these patients had many co-morbid medical conditions that could have played a role in these adverse events.
- There was a modest dose-dependent increase in mean residual volume among fesoterodine-treated groups, yet this increase remained below a group average of 50mL.
- Adverse events from the use of fesoterodine that led to discontinuation included dry mouth, constipation, dry eyes, urinary retention and urinary tract infection.
- Of the 5 patients who were reported to have died during this drug program development, one patient (#10672) in study SP582 died from cerebrovascular accident, the second patient (#10527) in study SP583 died from MI, the third patient (#10943) in study SP738 died due to metastastases to the liver, the fourth patient (#11184) in study SP738 died due to "sudden death" and fifth patient (#10618) died several months after completing study SP583 due to unknown causes. Four of the five deaths were considered by the investigators to be unrelated to study medication and the fifth (the "sudden death" case) was considered "unlikely related" to study medication.

Narratives for these 5 patients, who died during fesoterodine development program, are as follows:

Patient 10672, a 76-year old female who was randomized to treatment in Phase 2 study SP582 with fesoterodine 12mg/day, suffered a fatal stroke (CVA) on Day 83. In the opinion of the investigator this fatal SAE was not related to trial medication and had a

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