CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-030

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Division of Clinical Pharmacology 3** **Office of Clinical Pharmacology** **Tracking/Action Sheet for Formal/Informal Consults**

From: **Hyunjin Kim, Pharm.D., M.S.**			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 05/28/2008	IND No.: Serial No.:	NDA No.: 22-030 Serial No.:	DATE OF DOCUMENT **5/1/2008 and 6/18/2008**	
NAME OF DRUG **Fesoterodine fumarate**	PRIORITY CONSIDERATION		Date of informal/Formal Consult:	

NAME OF THE SPONSOR: Pfizer (distributor), Schwarz Pharma (manufacturer)

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (Pre-IND)	☒ OTHER *(SPECIFY BELOW)*:
☐ PHASE IV RELATED		[complete response to AE letter]

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☒ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☐ See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox	☐ Comments communicated in	☐ See submission cover letter
☐ Micro ☐ Pharmacometrics ☐ Others	meeting/Telecon. see meeting minutes	☐ OTHER *(SPECIFY BELOW)*:
(Check as appropriate and attach e-mail)	dated: [ ]	[ ]

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☒ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

This is a clinical pharmacology memo of complete response to FDA's "Approvable (AE)" action taken on NDA 22-030 (January 25, 2007).

Submission history

The sponsor submitted NDA 22-030 for fesoterodine fumarate, 4 and 8mg sustained release tablets on March 17, 2006 for the treatment of overactive bladder (OAB). This application received an approvable action pending sponsor's response to the following:

1. Pre-approval inspection of active pharmaceutical ingredient manufacturing facility, Schwarz Pharma LTd., located in Shannon, Ireland, which was not available during the review cycle.
2. Labeling revision. Reference is made to the revised labeling by FDA conveyed to the sponsor on January 24, 2007 for the basis for the future discussions. If additional information relating to the safety or effectiveness of fesoterodine becomes available, revision of the labeling may be required.

On May 1, 2008, the sponsor provided complete response to the AE letter with four modules (module 1, 2, 3 and 5)

- Module 1: revision of labeling conveyed to Schwarz biosciences on January 24, 2007.

- Module 2: common technical document summaries
- Module 3: quality, summary of the CMC information proposed to be included in the quality module of the complete response
- Module 5: five phase 1 clinical study reports and three study reports of uncontrolled clinical studies; Each study title and the conclusions by the sponsor are listed below.
    i. SP857: single-dose PK in Japanese subjects (Japan); "Randomized, double blind, placebo controlled, single site, dose escalation trial to investigate safety, tolerability and pharmacokinetics of fesoterodine after single oral administration of 4, 8, and 16mg doses in 12 young healthy male Japanese subjects"
        - Relative bioavailability of the pharmacologically active compound SPM 7605 was comparable for all dose levels in Japanese subjects. SPM 7605 and it metabolites (SPM 5509, SPM 7789, and SPM 7790) showed a similar plasma concentration-time profile with each dose level
    ii. SP877: single-dose proportionality (US); "Randomized, open-label, 2-fold crossover trial to investigate the dose-proportionality of fesoterodine administered as single dose administration of one 4mg tablet or one 8mg tablet in 24 healthy, male subjects" (Clinical trial report submitted in the previous NDA review cycle)
        - PK data show dose proportionality for the 2 dosage strengths (4mg and 8mg) investigated.
    iii. A0221004: multiple-dose (once daily for five days) PK in Japanese subjects (US); "A double blind, placebo controlled, multiple dose, randomized study to evaluate the safety and pharmacokinetics of fesoterodine sustained release tablets (SR) in Japanese healthy male subjects"
        - C_{max} and AUC_{τ} of SPM 7605, the active metabolite of fesoterodine, increased with dose after first and multiple-dose administrations and plasma concentrations reached steady state within 48 hours.
    iv. A0221015: multiple-dose (once daily for five days) PK in Korean subjects (Korea); "A double blind, placebo controlled, multiple dose, randomized study to evaluate the safety and pharmacokinetics of fesoterodine sustained release in Korean healthy male subjects"
        - Following single and multiple dose administrations of 4mg and 8mg once daily fesoterodine SR tablets to healthy Korean subjects, the PK profiles were consistent with those seen in Caucasian and Japanese subjects.
        - The systemic exposures of SPM 7605 increased approximately in the same proportion as the fesoterodine dose between 4mg and 8mg once daily.
    v. A0221044: single-dose proportionality and BE (US); "A phase 1, open label, randomized, single dose, 3 way crossover study to determine bioequivalence of two dose normalized E1 formulation doses as well as between formulations (E1 and F) of similar doses of fesoterodine SR tablets in healthy subjects"
        - Dose proportionality of SPM 7605 was established between the fesoterodine 4mg (E1) and fesoterodine 8mg (E1) SR tablets.
        - Bioequivalence was established between the fesoterodine 8mg (E1) and fesoterodine 8mg (F) SR tablets
    vi. SP669: Two-phase extension trial of SP668 to investigate the safety and tolerability of sustained release fesoterodine in subjects with overactive bladder: a double-blind phase followed by an open-label extension phase
    vii. SP738: Long-term open-label extension trial for subjects completing the phase 3 trial of fesoterodine (SP583) for the treatment of overactive bladder syndrome
    viii. SP739: Long-term open-label extension trial for subjects completing the Phase 3 trial of fesoterodine (SP584) for the treatment of overactive bladder syndrome

Background

Fesoterodine is a new chemical entity in the class of antimuscarinic agents. Fesoterodine itself is a relatively weak

pharmacokinetic and toxicokinetic studies have shown a rapid deesterification of fesoterodine to its hydroxy metabolite, SPM 7605. SPM 7605 is also formed in vivo by metabolization of tolterodine, which is approved for the treatment of symptoms of OAB.

Review of submissions

Module 1, labeling revision contains a modification of METABOLISM in the Clinical Pharmacology section. CYP2D6 was previously proposed to be a major metabolic pathway to further metabolize the major active metabolite, SPM 7605 to SPM 5509. In this current submission, the sponsor is proposing to add CYP3A4 metabolic pathway, which is responsible for metabolizing SPM 7605 to SPM 7789, along with CYP2D6 as two major metabolic pathways responsible to metabolize SPM 7605. This proposal was made based on the observation of the similar increase (2 to 2.5 fold) of the exposure of SPM 7605 in CYP2D6 poor metabolizers and subjects with CYP3A4 inhibition by ketoconazole (SP564, SP567, SP683, SP684 – studies submitted at the time of original submission; March 2006). The relevant studies will be reviewed to address the label revision proposed by the sponsor in the NDA review.

Sponsor suggests that the results of the five phase 1 clinical studies confirm that the PK of fesoterodine is dose proportional and independent of the ethnicity of subjects and that the formulation E1 is bioequivalent to the final commercial formulation (F).

- There was a change of engraving from [redacted] to "FT" to the final formulation F product. A dissolution comparison to bridge this change in engraving was found to be acceptable by the Office of New Drug Quality Assessment (ONDQA).

Table 1. Compositions of Fesoterodine 4mg SR Tablets

Formulation	B*	D	E	F
Fesoterodine fumarate				
Xylitol				
Lactose monohydrate				
Microcrystalline cellulose				
Lactose monohydrate				
Hypromellose [redacted]				
Hypromellose [redacted]				
Glyceryl behenate				
Talc				
[redacted]				
Total				

* Only 4 mg strength is available for formulation B

b(4)

Table 2. Compositions of Fesoterodine 8mg SR Tablets

Formulation	C*	D	E	F
Fesoterodine fumarate				
Xylitol				
Lactose monohydrate				
Microcrystalline cellulose				
Lactose monohydrate				
Hypromellose [redacted]				
Hypromellose [redacted]				
Glyceryl behenate				
Talc				
[redacted]				
Total				

* Only 8 mg strength is available for formulation C

b(4)

Table 3. Composition of Fesoterodine Fumarate Film Coated 4 mg SR Tablets Formulations E, E(1) and F

Formulation	E White film coated	E(1) [b] White film coated	F Light blue film coated
Fesoterodine fumarate			
Xylitol			
Lactose monohydrate (			
Hypromellose (			
Hypromellose (			
glyceryl behenate			
Talc			
Total			

b(4)

q.s.
a
b

Table 4. Composition of Fesoterodine Fumarate Film Coated 8 mg SR Tablets Formulations E, E(1) and F

Formulation	E White film coated	E(1) [b] White film coated	F Blue film coated
Fesoterodine fumarate			
Xylitol			
Lactose monohydrate			
Hypromellose (			
Hypromellose			
glyceryl behenate			
Talc			

b(4)

q.s.
a
b

Table 5. Film Coat Composition for Formulations E, E(1) and F

	Formulation E White film coated	Formulation E (1) White film coated	Formulation F Light blue film coated (4mg)	Formulation F Blue film coated (8mg)
Polyvinyl alcohol				
Titanium dioxide				
Talc				
Soya lecithin				
Indigo carmine aluminum lake				
Total				

b(4)

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