CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-206

MEDICAL REVIEW(S)

Deputy Director/Cross-Discipline Team Leader Review

Date	**September 29, 2008**
From	**George S. Benson, MD**
Subject	**Deputy Director/Cross-Discipline Team Leader Review**
NDA# **Supplement#**	**NDA 22-206** **000**
Applicant	**Watson Laboratories, Inc.**
Date of Submission	**December 13, 2008**
PDUFA Goal Date	**October 13, 2008**
Proprietary Name/ **Established name**	**Rapaflo/** **silodosin**
Dosage forms/Strength	**4 and 8 mg capsules**
Proposed Indication	**Treatment of the signs and symptoms of benign prostatic hyperplasia**
Recommendation	**Approval**

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Olivia Easley, MD
Statistical Review	Mahboob Sobhan, PhD
Pharmacology/Toxicology Review	Laurie McLeod-Flynn, PhD/ Lynnda Reid, PhD
CMC Review	Yichun Sun, PhD/Donna Christner, PhD
Microbiology Review	Robert Mellow, PhD/ James McVey, PhD
Clinical Pharmacology Review	Doanh Tran, RPh, PhD/ Sandhya Apparaju, PhD
DDMAC	Lisa Hubbard, PharmD/ Jialynn Wang, PharmD
DSI	Jose Tavarezpagan/ Constance Lewin, MD, MPH
CDTL Review	George S. Benson, MD
OSE/DMETS	Loreta Holmes, BSN, PharmD/ Carol Holquist, RPh
OSE/DDRE	Melissa Truffa, RPh, Paula Gish, RPh/Ann McMahon, MD, MS
IRTQT	Christine Garnett, PhD/ Norman Stockbridge, MD, PhD

1. **Introduction**
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1. Introduction

Currently approved medical therapy for the "treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)" includes alpha-1-adrenergic antagonists and 5-alpha reductase inhibitors, either alone or in combination. Alpha-1-adrenergic antagonists are believed to improve the symptoms of BPH by relaxing the prostatic and bladder neck smooth muscle and thereby reducing the degree of bladder outlet obstruction, although other mechanisms whereby these drugs exert their effect in improving symptoms in men with BPH may exist. Four alpha-1-adrenergic antagonists are currently approved in the United States for the treatment of BPH: terazosin (Hytrin®), doxazosin (Cardura®), tamsulosin (Flomax®), and alfuzosin (Uroxatral®).

Silodosin (proposed trade name RAPAFLO™) is a new molecular entity alpha-1-adrenergic antagonist. The proposed indication is the "treatment of the signs and symptoms of benign prostatic hyperplasia (BPH);" the NDA was submitted on December 11, 2007. Silodosin (Urief®) was approved in Japan on January 23, 2006, for essentially the same indication - treatment of "bladder outlet obstruction associated with BPH." Silodosin is also being developed for the treatment of BPH in Europe, [redacted] by Recordati, S.p.A.,

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[redacted]

2. Background

The pertinent regulatory history of silodosin is provided in the sponsor's table (Table 1) below:

Table 1. Regulatory History

Table 2.1 Presubmission Regulatory Activity, NDA 22-206		
Date	Activity	Comments from FDA
August 13, 1998	IND opened for BPH indication	
July 3, 2003	FDA Clinical review comments regarding Phase 3 clinical plans	An EOP2 meeting would be necessary to discuss dose selection for Phase 3 clinical development
February 10, 2005	EOP2 meeting	Determination that no preclinical issues were outstanding and that data support initiation of Phase 2 Recommended lower dose of silodosin for special population
May 2, 2005	FDA Phase 3 clinical protocol review comments	Investigation of only one dose (8 mg) requires additional discussion Suggestion that serum prolactin data be obtained
May 23, 2005	Corrections to the EOP2 meeting minutes	As a result of additional discussions, consensus of testing only one dose (8 mg) in Phase 3 was reached, with the risks of this approach outlined.
July 22, 2005	Clinical guidance teleconference	Suggestions for prolactin and thyroid monitoring provided
August 12, 1005	Clinical guidance teleconference	Agreement for not including thyroid ultrasound and an age-matched control group as part of thyroid monitoring during Phase 3
January 5, 2006	Watson telephone contact report	A reduction in sample size for the Phase 3 studies was acceptable to the Division
December 1, 2006	FDA clinical review comments on the thorough QTc study	Multiple suggestions to the thorough QTc study design were provided
January 19, 2007	FDA clinical review comments for the statistical analysis plans for the Phase 3 protocols	Division commented that they consider the primary endpoint for the Phase 3 studies to be the IPSS and not the IPSS-1 (IPSS-1 includes an eighth quality of life question).
March 16, 2007	FDA clinical review comments for the SAPs for the Phase 3 protocols	Division agreed that the SAPs for the Phase 3 studies were acceptable.
March 29, 2007	Clinical guidance teleconference regarding design of thorough QT study	Supratherapeutic dose of 24 mg was recommended for the thorough QTc study The Division recommended a lower therapeutic dose (4 mg) for use in special populations based on pharmacokinetic data
July 23, 2007	Pre-NDA meeting	Agreement to supply available European safety data at time of filing without integration into U.S. safety database Agreement on the filing of a pediatric [redacted], with the NDA.

Source: NDA 22-206 ser 000, Table 2.5-1 in Clinical Overview.

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NDA 22-206 was submitted on December 13, 2007. A "74-day" letter detailing review issues was sent to the sponsor on February 25, 2008.

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 substance and drug product. Therefore, from a CMC perspective, this NDA is recommended for "Approval" with pending review on labels, and Establishment Evaluation." The container and carton labels are acceptable.

The CMC reviewer also states that "the proposed expiration date of 24 months for the capsules (4 mg and 8 mg) is supported by the stability data."

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. At the time of writing this review, no report has been received from the inspection of all manufacturing facilities. (see Addendum dated October 8, 2008). Stability testing supports an expiration date of 24 months. With the exception of the manufacturing site inspections, there are no outstanding CMC issues.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer concluded that the nonclinical data support an approval action for this NDA.

Three potentially significant issues were addressed by the pharmacology/toxicology reviewer during the review of the nonclinical data submitted for silodosin.

a. Thyroid Follicular Cell Tumors in Rats

In a 2-year oral carcinogenicity study in rats, an increased incidence of thyroid follicular cell tumors was seen in male rats receiving doses of 150 mg/kg (approximately 8 times the exposure of the maximum recommended human dose via comparative silodosin AUC). In addition, silodosin induced stimulation of TSH secretion in the male rat and decreased circulating levels of thyroxine (T4). The pharmacology/toxicology reviewer states that "Evidence of a mechanism in rats exists that may not be relevant to humans: In rats, drug induced thyroid tumors are reported to be induced by increased UDP-GT levels (a finding specific to rodents) and resulting alterations of thyroid hormones. Studies using silodosin were performed and confirmed the presence of this mechanism in rats after silodosin administration. No evidence of an effect of silodosin on thyroid hormones or on prolactin levels was observed in adult male clinical trial participants."

In the Phase 3 clinical trials, thyroid physical examination and measurement of serum thyroid function tests (free and total T4, TSH, T3) were performed at screening and end of treatment. Thyroid function tests were also monitored during the open-label extension study. There was no evidence of an effect of silodosin on thyroid hormones or on thyroid physical examination over the one year duration of the trials.

b. Increased Incidence of Mammary Gland Adenoacanthoma and Adenocarcinomas in Female Mice

In a 2-year oral carcinogenicity study in mice administered silodosin doses up to 200 mg/kg/day in males and 400 mg/kg/day in females, there were no significant tumor findings in male mice. Female mice treated for 2 years with doses of 150 mg/kg/day or greater (approximately 29 times the maximum recommended human dose via AUC) had statistically significant increases in the incidence of mammary gland adenoacanthomas and adenocarcinomas ($p < 0.001$). The increased incidence of mammary gland neoplasms in female mice was considered secondary to silodosin-induced hyperprolactinemia.

The DRUP pharmacology/toxicology reviewer believes that these findings in mice are not considered clinically relevant because: i) the drug is not indicated in females, ii) there is a sufficient safety margin between the dose at which tumors occurred and the clinical dose, and iii) induction of mammary adenomas and carcinomas has been noted in mice following administration of other drugs of this class without clinical findings in adult male humans.

In the two Phase 3 clinical trials, serum prolactin levels were measured at baseline and at week 12. No increase in serum prolactin levels was observed. In addition, breast examinations were performed and there was no increase in breast examination abnormalities among silodosin-treated patients.

c. Effects on male rat fertility

Treatment of male rats with silodosin for 15 days resulted in decreased fertility at the high dose of 20 mg/kg/day (approximately 2 times the maximum recommended human dose) which was reversible following a two week recovery period. No effect was observed at 6mg/kg/day. The pharmacology/toxicology reviewer notes that the high dose effects are similar to the nonclinical effects reported for other drugs in this class. These effects in rats were reversible. It is not known if the effect is species-specific and if these findings have any clinical relevance. This information should be included in the product label with a statement that clinical relevance is unknown.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding nonclinical issues that preclude approval.

5. Clinical Pharmacology

The clinical pharmacology review team concluded that NDA 22-206 is "acceptable from a Clinical Pharmacology perspective, provided the labeling comments are adequately addressed."

The clinical pharmacology reviewer's labeling recommendations are summarized below:

a. CYP3A4 inhibitors: Silodosin should not be used in patients taking strong inhibitors of CYP3A4. Caution should be exercised when co-administering silodosin with moderate CYP3A4 inhibitors.

Ketoconazole co-administration significantly increased the C_{max} and AUC of silodosin and its major metabolites. In two phase I drug-drug interaction studies, co-administration of silodosin with ketoconazole, a potent CYP3A4 inhibitor that also inhibits P-glycoprotein (P-gp), increased silodosin AUC and C_{max} by 3.2 and 3.8-fold, respectively. The sponsor initially proposed that

. I agree with the primary medical officer and the clinical pharmacology reviewer that strong CYP3A4 inhibitors should be contraindicated in patients taking silodosin.

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- In study KMD3213-UK01-97 in which healthy adult male volunteers received single doses of 4 mg, 12 mg or 16 mg of silodosin, two of nine subjects assigned to the 16 mg dose group experienced syncope after receiving silodosin. Their systolic blood pressures were 80 and 85 mmHg, respectively.

- In a ketoconazole drug interaction study (trial KMD-306-UK), two of sixteen subjects experienced orthostatic hypotension following concomitant dosing of silodosin 4 mg with ketoconazole 200 mg.

- In a maximum tolerated dose study (study SI05008) performed in healthy adult male volunteers, all five subjects assigned to the 16 mg dose group met orthostatic pulse criteria (change in HR>20bpm) at least one time point during dosing. There were also 5 events of symptomatic postural hypotension in the 16 mg dose group.

The observed effects of ketoconazole on the pharmacokinetics of silodosin may not be due entirely to ketoconazole's effect on CYP3A4 because of the following reasons:

- Ketoconazole has the potential to inhibit the efflux transporter P-glycoprotein (P-gp). Silodosin is a P-gp substrate. Inhibition of P-gp efflux transporter in the gastrointestinal tract could increase drug absorption. The in vivo potency of ketoconazole to inhibit P-gp is, however, not well established.
- In vitro studies indicate that the major metabolites of silodosin are not generated through CYP3A4.
- The mean elimination T1/2 was similar in the presence or absence of ketoconazole co-administration.
- Ketoconazole has been shown in vitro to inhibit the enzyme UGT2B7, which is responsible for metabolism of silodosin to the major metabolite KMD-3213G. It is not known if in vivo administration of 400 mg ketoconazole inhibits UGT2B7.

A separation of the various possible effects of ketoconazole is not possible at this time. Because of the risk of hypotension, however, I agree that concomitant use of strong CYP3A4 inhibitors and silodosin should be contraindicated, despite the fact that the exact mechanism(s) which lead to increased silodosin exposures are not clear.
The effect of moderate CYP3A4 inhibitors on silodosin metabolism was not evaluated. I agree with the medical officer and clinical pharmacologist's recommendation that "caution should be exercised" when co-administering silodosin with moderate CYP3A4 inhibitors.

b. Silodosin should not be used in patients with severe renal impairment. The dose should be lowered to 4 mg once daily in patients with moderate renal impairment. No dose adjustment is needed in patients with mild renal impairment.

A clinical pharmacology study (study KMD-309) compared the pharmacokinetics of a single oral dose of 4 mg silodosin in Japanese subjects with moderate renal dysfunction (Ccr 27-49 mL/min) to Japanese subjects with normal renal function. In subjects with moderate renal dysfunction, plasma concentration of silodosin increased approximately three-fold (3.11 for C_{max} and 3.22 for AUC). Based on these data the sponsor recommends that [redacted]. I agree with the recommendation of the medical officer (see pages 78 and 79 of medical officer review) and the clinical pharmacology reviewer that the dose of silodosin be reduced to 4 mg daily in patients with moderate renal impairment. b(4)

No data exist for the safety of silodosin in patients with severe renal insufficiency and use of silodosin in this patient population should be contraindicated. No dosage adjustment is needed in patients with mild renal impairment.

c. Hepatic impairment

In a Phase I study of the effects of hepatic dysfunction on silodosin metabolism, silodosin exposure was slightly lower in subjects with moderate liver dysfunction (Child-Pugh score 7-9) compared to age and weight-matched controls (total silodosin C_{max} and AUC decreased by 0.8). The sponsor does not recommend a dose adjustment for subjects with moderate hepatic dysfunction. I agree with the medical officer and clinical pharmacologist's recommendation that 8 mg silodosin once daily is an acceptable dose for patients with mild to moderate hepatic impairment. There are no data on the safety or pharmacokinetics of silodosin in subjects with severe hepatic impairment. Therefore, silodosin should be contraindicated in this patient population.

d. No dose adjustment is recommended for age of the patient.

e. Patients should be advised to take silodosin with food.

f. P-glycoprotein (P-gp) inhibitors: *In vitro* studies indicated that silodosin is a P-gp substrate. A drug interaction study with a strong P-gp inhibitor such as cyclosporine or itraconazole has not been conducted. A drug interaction study with ketoconazole, a CYP3A4 inhibitor that may also

inhibit P-gp, showed significant increase in exposure to silodosin. Silodosin should not be used concomitantly with strong P-gp inhibitors (e.g. cyclosporine or itraconazole).

g. Co-administration of silodosin did not significantly affect the PK of digoxin, a P-gp substrate with a narrow therapeutic index.

h. *In vitro* studies indicated that silodosin administration is not likely to inhibit the activity of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 or induce the activity of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4, and P-gp.

I agree with the clinical pharmacologist and medical officer that the above should be included in labeling.

6. **Clinical Microbiology**

The microbiology reviewer recommended approval of this NDA. There are no unresolved microbiology issues.

7. **Efficacy/Statistics**

The sponsor submitted one controlled phase 2 study and two primary phase 3 studies (all three trials conducted in the United States) which enrolled 1,187 patients with benign prostatic hyperplasia to support efficacy. The phase 2 study evaluated a 4 mg and an 8 mg dose; the two identically designed phase 3 studies evaluated only an 8 mg dose. The two primary phase 3 studies (Trial #'s 4009 and 4010) were identically designed, multicenter, 12-week, placebo controlled trials. Patients completing studies 4009 and 4010 could enter a 9-month open label safety extension trial (4011).

Primary endpoints:

The primary endpoint in both trials was the change from baseline to week 12 (using LOCF) in the International Prostate Symptom Score (IPSS) total score.

Secondary endpoint:

A key secondary endpoint in both trials was the change from baseline to week 12 (using LOCF) in the maximum urinary flow rate (Q_{max}).

Key inclusion criteria included:

- Males 50 years of age or older on day of consent and who, in the opinion of the Investigator, were in good general health on the basis of medical history, physical examination, and laboratory results
- At Visits 1 and 3, had a Q_{max} (peak urine flow rate) between 4 and 15 mL/sec, with a minimum voided volume of $\geq$125 mL
- At Visits 1 and 3, had an IPSS of $\geq$13.

Withdrawals:

Of the 461 patients randomized in trial 4009, 416 completed the trial and 45 discontinued prematurely. Discontinuation due to adverse events was more common among silodosin patients. Causes of premature discontinuation in trial 4009 are shown in Table 2.

Table 2. Premature discontinuation in trial 4009.

Table B.2. SI04009 Patient Disposition (Safety Population)

	Treatment Group		Overall N=461
	Placebo N=228	Silodosin N=233	
Number of Patients n (%)			
Completed	214 (93.9)	202 (86.7)	416 (90.2)
Discontinued	14 (6.1)	31 (13.3)	45 (9.8)
Discontinuation due to:			
Adverse Event	6 (2.6)	20 (8.6)	26 (5.6)
Protocol Violation	3 (1.3)	2 (0.9)	5 (1.1)
Voluntary Withdrawal	4 (1.8)	1 (0.4)	5 (1.1)
Lack of efficacy	0	2 (0.9)	2 (0.4)
Lost to follow-up	0	4 (1.7)	4 (0.9)
Investigator recommendation	0 (0)	1 (0.4)	1 (0.2)
Other	1 (0.4)	1 (0.4)	2 (0.4)

Source: NDA 22-206, study report SI04009, table 14.1.2

Of the 461 patients randomized in Trial 4010, 24 patients withdrew from the placebo group and 22 from the silodosin group (Table 3).

Table 3. Premature discontinuation in trial 4010.

C.2 SI04010 Patient Disposition (Safety Population)

	Treatment Group		Overall N=461
	Placebo N=228 n (%)	Silodosin N=233 n (%)	
Discontinuation due to:			
Adverse Event	4 (1.7)	10 (4.3)	14 (3.0)
Protocol Violation	0	1 (0.4)	1 (0.2)
Voluntary Withdrawal	10 (4.4)	5 (2.1)	15 (3.2)
Lack of efficacy	2 (0.9)	0	2 (0.4)
Lost to follow-up	3 (1.3)	2 (0.9)	5 (1.1)
Investigator recommendation	0	0	0
Other	5 (2.2)	4 (1.7)	9 (1.9)

From NDA 22-206, study report SI04009, table 14.1.2

The results of the primary efficacy analysis (IPSS) for the two primary phase 3 trials are shown in Tables 4 and 5.

Table 4. IPSS Results in Trial 4009.

Table B.5. Change from baseline in IPSS total score (mITT), SI04009

Visit	Statistic	Placebo N=228	Silodosin (N=233)
Week 0 (baseline)	Mean (SD)	21.4 (4.91)	21.5 (5.39)
Week 12 (LOCF)	Mean (SD)	17.7 (6.55)	15.0 (6.96)
Change	Mean (SD)	**-3.6 (5.85)**	**-6.5 (6.73)**
p-value		<0.001	

Source: NDA 22-206 ser 000, SI04009 study report, Table 14.2.1-1

Table 5. IPSS Results in Trial 4010.

Table C.3. Summary of Change from Baseline in IPSS Total Score by Treatment Group and Visit (mITT)

Visit	Statistic	Placebo N=229	Silodosin N=233
Week 0 (baseline)	Mean (SD)	21.2 (4.92)	21.2 (4.88)
Week 12 (LOCF)	Mean (SD)	17.7 (6.95)	14.9 (6.82)
Change	Mean (SD)	-3.4 (5.83)	-6.3 (6.54)
p-value		<0.001	

Source: NDA 22-206 ser 000, SI04010 study report, Table 14.2.1-1

The MITT population was agreed upon for the statistical analysis and was defined as all randomized patients who received at least one dose of study drug and, at a minimum, provided IPSS data at baseline. The results of the primary endpoint in both primary efficacy studies were highly statistically significant and are, in general, comparable to data observed in trials with other alpha -1-adrenergic antagonists. Currently, the IPSS is used as the primary efficacy endpoint in all trials evaluating drugs for treatment of the signs and symptoms of BPH.

Changes in the maximum urinary flow rate (Q_{max}) was a pre-specified secondary endpoint. This endpoint has been included in labeling for previously approved alpha-1-adrenergic antagonists for the treatment of BPH. Q_{max} changes for trials 4009 and 4010 are shown in Table 6.

Table 6. Q_{max} changes seen in Trials 4009 and 4010.

Table 6.7. Summary of Change from Baseline to week 12 (LOCF) in Qmax – Phase 3 studies SI04009 and SI04010

Study	Visit	Statistic	Placebo	Silodosin	p-value
SI04009			N=228	N=233	
	Week 12 (LOCF)	Mean (SD)	+1.2 (3.81)	+2.2 (4.31)	0.0060
SI04010			N=229	N=233	
	Week 12 (LOCF)	Mean (SD)	+1.9 (4.82)	+2.9 (4.53)	0.0431

Source: NDA 22-206 ser 000, SI04009 study report, Table 11.4.1-7 and SI04010 study report, Table 11.4.1-7

The baseline Q_{max} values for the 4009 study were 9.0 cc/sec in both the placebo and silodosin groups. For study 4010, the baseline in the placebo group was 8.7 cc/sec and the baseline in the silodosin group was 8.4 cc/sec.

Although no studies comparing silodosin with other alpha-adrenergic antagonists have been performed, the changes seen in IPSS and Q_{max} appear comparable to the currently approved alpha-adrenergic antagonists approved for the treatment of benign prostatic hyperplasia.

In phase 2 study USO21-99, 4 and 8 mg silodosin doses were compared to placebo. The IPSS and Q_{max} are shown in the Tables 7 and 8.

Table 7. Change from baseline in IPSS in Phase 2 trial USO21-99.

Table A.3 Mean Change from Baseline in AUA-SS, US021-99

Treatment Group	N	Mean Change from Baseline at end-of-study (SD)	p-value (vs. placebo)
8 mg silodosin	90	-6.8 (5.8)	0.0018
4 mg silodosin	88	-5.6 (5.5)	0.0355
Placebo	83	-4.0 (5.5)	

Source: NDA 22-206 ser 000, US021-99 study report, Table 5.1

Table 8. Change from baseline in Q_{max} in Phase 2 trial USO21-99.

Table A.4 Mean Change from Baseline in Qmax

Treatment Group	N	Mean Change from Baseline at end-of-study (SD)	p-value (vs. placebo)
8 mg silodosin	90	+3.4 (5.7)	0.0174
4 mg silodosin	88	+2.9 (4.0)	0.0966
Placebo	83	+1.5 (4.4)	

Source: NDA 22-206 ser 000, US021-99 study report, Table 5.2

The 4 and 8 mg efficacy data demonstrated in Phase 2 study USO-99 (as well as safety results) support the use of the 8 mg dose.

Statistical review:

The statistical reviewer concluded that "The results support the efficacy of Rapaflo 8 mg once daily in treating the signs and symptoms of benign prostatic hyperplasia as measured by the International Prostate Symptom Score (IPSS) and maximum urine flow rate (Q_{max}). In two US clinical trials, treatment with Rapaflo 8 mg resulted in statistically significant improvement in IPSS ($P<0.01$) and Q_{max} ($p<0.01$) compared to placebo. From a statistical perspective, this application provided adequate data to support the efficacy of Rapaflo 8 mg once a day for the treatment of BPH."

Efficacy summary:

Two adequately controlled trials (trials 4009 and 4010) showed statistically significant changes in the primary endpoint (IPSS). I believe that the results of these trials demonstrate that silodosin is efficacious in the treatment of the signs and symptoms of BPH.

7. **Safety**

A total of 1,371 subjects or patients were exposed to silodosin in the studies summarized in the NDA. In the clinical pharmacology studies conducted for the NDA, there were 474 patients exposed to daily doses of silodosin of 0.1 to 48 mg, for 1 to 21 days. These trials were conducted in Japan, Europe and the U.S. In the US Phase 2/3 studies, 897 patients were exposed to daily doses of 8 mg silodosin (the proposed therapeutic dose), of which 486 patients were exposed for 26 weeks or more, and 168 patients were exposed for 52 weeks or more.

Three controlled Phase 2/3 studies have been conducted with silodosin in the US in 1,187 patients with BPH. Phase 2 study **KMD 3213-US021-99** enrolled 264 patients (N=90 on 8 mg silodosin qd; N=88 on 4 mg qd). Phase 3 studies **SI04009** and **SI04010** enrolled 461 and 462 patients, respectively (N=466 on silodosin 8 mg daily). In addition, of the 1,187 patients enrolled in these trials, 661 patients continued into a 9-month open-label safety study (**SI04011**) of silodosin 8 mg qd.

Additional safety data in 1,858 patients (901 on silodosin) come from six Japanese Phase 2/3 studies and a single European Phase 3 study.

The safety review concentrated on the three United States phase 2/3 studies and on the open label extension study. Review of the Japanese (Phase 1 through 3) and European Phase 3 clinical trials was limited to deaths and significant safety signals identified during the primary medical officer review.

Deaths:

In the four silodosin Phase 2/3 studies (including the open-label safety extension study) performed in the United States there were three deaths, two in the open-label safety extension study and one in a placebo treated patient. The narrative summaries of these two patients were reviewed and the deaths do not appear to be related to silodosin therapy.

No deaths were reported in the U.S. phase 1 studies, the Japanese clinical trials, or in the European phase 3 trial.

Serious adverse events (SAEs):

In the 2 controlled phase 3 studies (4009 and 4010), seventeen serious adverse events (SAEs) were reported in 13 patients (6 on silodosin, 7 on placebo) during the double-blind treatment period. These SAEs are shown in Table 9. No SAEs were reported in the United States controlled Phase 2 study.

Table 9. Serious adverse events in placebo-controlled trials 4009 and 4010.

Table 7.1 Serious Adverse Events Occurring in US controlled Phase 3 trials (SI04010 and SI04009)

Patient ID	SAE (s)	Pt medical history	Time on drug at onset of AE	Action Taken	Relation to therapy (investigator assessment)
Silodosin Cases					
SI04009/ 136019	Acute myocardial infarction (MI)	65M h/o CAD, COPD	23 days	Drug d/c'd	unrelated
	Congestive heart failure				
	Enterococcal bacteremia				
	Respiratory failure				
SI04009/ 101027	Cervical radiculopathy	68M h/o htn, b/l OA (hips)	20 days	Treatment interrupted	unrelated
SI04009/ 112028	Acute MI	70M h/o hypothyroidism	74 days	Drug d/c'd	Unrelated
SI04010/ 272046	Syncope	85M h/o DM, PVD, HTN, CAD	2 days	Drug d/c'd	Related
SI04010/ 259003	Complete heart block	69M h/o DM, HTN, hi chol, type 1 second degree AV block	39 days	None (drug not d/c'd)	unrelated
SI04010/ 295024	Carotid artery stenosis aggravated	63M h/o carotid stenosis, DM, HTN, CAD	80	None	Unrelated
Placebo cases					
SI04010/ 273015	Rotator cuff tear	60M	3 days	none	unrelated
SI04010/ 278045	Bacterial enterocolitis	60M h/o hi chol	67 days	interrupted	Unrelated
	Acute renal failure				Unrelated
SI04010/ 285011	Removal of vocal cord lesion	60M h/o vocal cord lesion, anxiety	18 days	Interrupted	Unrelated
SI04010/ 287010	Suicidal ideation	62M h/o depression	7 days	Discontinued	Unrelated
SI04009/ 103008	Small bowel obstruction	74M h/o CAD, PVD	62 days	Discontinued	Unrelated
	Myocardial infarction				unrelated
SI04009/ 105013	Gastrointestinal bleed	55M	Occurred during placebo run-in	Interrupted	unrelated
SI04009/ 106028	diverticulitis	58M h/o diverticulitis		Discontinued	Unrelated

Narratives for all SAEs were reviewed by the primary medical officer. Only the case of syncope (SI04010-272046) appears to be possibly related to study drug.

Serious adverse events in the phase 3 open-label safety extension (trial 4011):

In study 4011, the 40-week open-label extension study, 29 patients experienced 35 serious adverse events: osteoarthritis (4 events); lung neoplasm malignant (3 events); diverticulitis (2 events); hip arthroplasty (2 events); atrial fibrillation (2 events); prostate cancer (2 events); pulmonary embolism (2 events); myocardial infarction (2 events); and one event each of abdominal aortic aneurysm repair; back injury; status-post fall injury/severe concussion; knee arthroplasty; nerve root lesion; deep vein thrombosis; spinal laminectomy; arrhythmia, arthralgia; squamous cell carcinoma (throat); acute gastritis; pain in extremity; femoral artery occlusion; transient ischemic attack; lobar pneumonia; and aggravated carotid artery stenosis. None of the SAEs were considered by the investigator to be related to silodosin.

Narrative summaries of the SAE's were reviewed by the primary medical officer. A relationship to silodosin could be reasonably excluded in nearly all cases except that of patient 126031 (s/p fall injury/severe concussion) where it is not possible to determine the cause of the fall (i.e., syncope) from the information provided.

Withdrawals secondary to adverse events:

In the integrated U.S. safety database (controlled and uncontrolled Phase 2/3 trials) 127 patients discontinued prematurely due to an adverse event. Retrograde ejaculation, which occurred in 5.5% of silodosin patients, was the most common adverse event (AE) leading to discontinuation.

In U.S. controlled Phase 3 trials, dropouts due to AEs were more common among silodosin-treated patients than those on placebo (12.9% versus 4.3%, respectively). The most common AEs leading to discontinuation among silodosin patients in these trials are shown in Table 10.

Table 10. Adverse events leading to early discontinuation in trials 4009 and 4010 combined.

Table 7.2. AEs leading to early discontinuation, US Controlled Phase 3 trials

Adverse Event (Preferred term)	Silodosin N=466	Placebo N=457
Retrograde ejaculation	13 (2.7%)	0
Dizziness	2 (0.4)	1 (0.2)
Orthostatic hypotension	2 (0.4)	0
Syncope	1 (0.2)	0

Source: NDA 22-206 ser 000, ISS, Table 2.2.1-12

All of the adverse events in the above table which lead to early discontinuation are recognized to occur with alpha-adrenergic antagonists.

In the open-label safety extension (4011), eighty-six patients (13.0%) discontinued prematurely due to an adverse event emerging during the open-label period. The most common AEs resulting

in discontinuation were retrograde ejaculation (4.8%), diarrhea (0.8%), libido decreased (0.6%), dizziness (0.5%), and lung neoplasm malignant (0.5%). The events of retrograde ejaculation, diarrhea, libido decreased, and dizziness were considered by the study investigator to be related to study drug.

A single patient in this study discontinued due to the adverse event of intra-operative floppy iris syndrome (IFIS). This condition has been seen in association with alpha-adrenergic antagonist use and information relating to IFIS will be included in the Rapaflo labeling. IFIS is included in the labeling of all currently approved alpha-1-adrenergic antagonists indicated for the treatment of BPH.

Common adverse events:

From all four US Phase 2/3 studies, treatment-emergent adverse events occurring in ≥1% of patients are shown in Table 11.

Table 11. Common Treatment-Emergent Adverse Events.

Table 7.3 Summary of Treatment-Emergent Adverse Events Occurring in >1% of Patients (All U.S. Controlled and Uncontrolled Trials)

Adverse Event – Preferred Term	Percentage (N=897)
retrograde ejaculation	31.9
diarrhea	4.8
dizziness	3.8
nasopharyngitis	3.8
orthostatic hypotension	3.2
headache	2.7
nasal congestion	2.7
URI	2.5
PSA increased	2.3
arthralgia	2.2
hypertension	2.0
Sinusitis	1.8
Back pain	1.6
Cough	1.4
Erectile dysfunction	1.4
Libido decreased	1.4
Urinary tract infection	1.4
Influenza	1.3
Abdominal pain	1.2
Bronchitis	1.1
Sinusitis	1.1
Blood urine present	1.0
GGT increased	1.0
Nausea	1.0
Pharyngolaryngeal pain	1.0

Source: NDA 22-206 ser 000, Table 2.5.3

Treatment-emergent adverse events that occurred in ≥2% of patients receiving silodosin in Phase 3 controlled trials, and at an incidence numerically higher than that of placebo are shown in Table 12.

Table 12. Treatment-emergent adverse events that occurred in ≥2% of patients receiving silodosin in Phase 3 controlled trials

U.S. Controlled Phase 3 trials

Adverse Event – preferred term	**Silodosin N=466 n (%)**	**Placebo N= 457 n (%)**
Retrograde ejaculation	131 (28.1)	4 (0.9)
Dizziness	15 (3.2)	5 (1.1)
Diarrhea	12 (2.6)	6 (1.3)
Orthostatic hypotension	12 (2.6)	7 (1.5)
Headache	11 (2.4)	4 (0.9)
Nasopharyngitis	11 (2.4)	10 (2.2)
Nasal congestion	10 (2.1)	1 (0.2)

Source: NDA 22-206 ser 000, Table 2.5.4

The majority of common treatment-emergent adverse events seen with silodosin (dizziness, orthostatic hypotension, nasal congestion) are comparable to those reported for other approved alpha-1-adrenergic receptor antagonists. The incidence of retrograde ejaculation seen with silodosin is higher than that reported in clinical trials of currently marketed alpha-1-antagonists. This adverse event is, however, not serious and is reversible with drug discontinuation.

Laboratory safety parameters:

Hematology:

In both controlled Phase 3 studies and the open-label extension study, there was no significant difference in mean change from baseline to endpoint in any hematology parameter between placebo and silodosin treatment groups.

Chemistry:

In controlled Phase 3 trials, more silodosin patients than those on placebo experienced a shift from "normal" at baseline to "high" on treatment in serum AST, GGT and creatinine (Table 13).

Table 13. Shifts of chemistry laboratory values from "normal" to "high" during treatment.

Table 7.6 Summary of Patients experiencing a shift in serum chemistry parameters from "normal" to "high" during treatment – U.S. Controlled Phase 3 trials (Safety Population)

Analyte	Study Visit	placebo	silodosin
AST	>0-6 weeks	8/435 (1.8%)	12/432 (2.8%)
	>6 weeks	5/417 (1.2%)	12/414 (2.9%)
	Last observation	5/442 (1.1%)	13/452 (2.9%)
Creatinine	>0-6 weeks	5/435 (1.1)	3/423 (0.7%)
	>6 weeks	4/417 (1.0)	8/416 (1.9%)
	Last observation	4/442 (0.9%)	8/454 (1.8%)
GGT	>0-6 weeks	11/435 (2.5%)	12/432 (2.8%)
	>6 weeks	11/417 (2.6%)	17/416 (4.1%)
	Last observation	12/442 (2.7%)	18/454 (4.0%)

Hepatic events:

Line listings from controlled Phase 3 studies 4009 and 4010 were searched for subjects with a post-treatment AST or ALT value >3-5 X ULN, >5X ULN or >10X ULN, GGT>2X ULN or a total bilirubin value >2X ULN. Results are shown in Table 14.

Table 14. Patients meeting pre-specified criteria for abnormal liver function tests in trials 4009 and 4010.

Table 7.12 Subjects meeting pre-specified criteria for abnormal liver function test, U.S. Controlled Phase 3 Studies (Safety Population)

Analyte	Degree above upper limit of normal	Silodosin N=457	Placebo N=466
AST (0-37 U/L)	3-5X ULN	0	0
	>5X ULN	1	0
	>10X ULN	0	0
ALT (0-47 U/L)	3-5X ULN	0	0
	>5X ULN	0	0
	>10X ULN	0	0
GGT (0-51 U/L)	>2XULN	1	1
T.Bili 0-1.1 ug/dL)	>2X ULN	2	1

Source: NDA 22-206 Ser 005, section 5.3.5.3.3, silodosin effects on liver function tests

The four cases in silodosin treated patients were reviewed by the primary medical officer (see medical officer review pages 46-49) and the relationship to silodosin use was deemed unlikely. I agree with the medical officer's assessment.

None of the patients had abnormal liver function tests that met Hy's law criteria (transaminase >3X ULN combined with increased bilirubin to at least 2X ULN).

Two silodosin patients (pt #250024 and #121002) experienced an increase in total bilirubin to >2X ULN during the study. However, both subjects had elevated total bilirubin at screening (2.0 mg/dl in each subject). Peak total bilirubin was 2.5 mg/dl (subject 250024) and 2.8 mg/dL (subject 121002). Neither patient experienced an increase in serum transaminase or GGT.

Liver function abnormalities in US open label trial 4011:

Safety data from study 4011 were searched for patients meeting the following criteria: AST or ALT >3-5 X ULN, >5X ULN or >10X ULN, GGT>2X ULN or a total bilirubin value >2X ULN. Results are shown in Table 15.

Table 15. Patients meeting pre-specified criteria for abnormal liver function tests in trial 4011.

Table 7.14 Subjects meeting pre-specified criteria for abnormal liver function test, U.S. Open-Label Safety Extension Study (SI04011)

Analyte	Degree above upper limit of normal	Silodosin N=661
AST (0-37 U/L)	3-5X ULN	2
	>5X ULN	1
	>10X ULN	0
ALT (0-47 U/L)	3-5X ULN	2
	>5X ULN	0
	>10X ULN	0
T.Bili 0-1.1 ug/dL)	>2X ULN	2

These cases were further reviewed by the medical officer. Because of the limited information available, it is not possible to determine causality in these patients.

Liver function abnormalities in European and Japanese studies:

The sponsor submitted preliminary laboratory data from a completed European Phase 3 study in which subjects were randomized to receive silodosin 8 mg (N=390), tamsulosin 0.4 mg (N=393) or placebo (N=194) once daily for 12 weeks. Liver function test data were reviewed. A slightly greater percentage of silodosin subjects experienced a shift in serum AST and ALT than those on placebo (Table 16).

Table 16. Patients experiencing a shift from normal to high in liver function tests in European study.

Table 7.17 Subjects experiencing laboratory parameter shift from normal at baseline to high post-baseline, European Phase 3 trial

Analyte	Silodosin (N=390) N (%)	Placebo (N=194) N (%)
AST	4 (1.0)	1 (0.5)
ALT	12 (3)	3 (1.5)
T. Bili	13 (3.3)	9 (4.6)

No subject on silodosin or placebo had post-treatment elevations in serum transaminase >3X ULN or total bilirubin >2X ULN in the European Phase 3 study.

No silodosin subjects in the Japanese Phase 3 study developed transaminase elevation >3X ULN.

Post marketing liver abnormality data:

The sponsor has been submitting serious, unexpected adverse post-marketing event reports to the IND. As of July 30, 2008, there have been seven such reports involving hepatic function disorder, all occurring outside the U.S. These cases are reviewed in the primary medical officer review (pages 48-54).

The Division of Pharmacovigilance II (DPV II) was consulted to review the post-marketing hepatic adverse event reports involving silodosin. Six cases were forwarded to DPV II. The seventh, patient ID 2008-04048, was received later and was not reviewed by DPV II. The DPV II consultant's conclusions follow:

> Two cases of jaundice (cases #2006-05221, #2006-04503) were possibly due to gallstones. Both reported a rapid improvement of liver function tests (less than 2 weeks) after silodosin discontinuation, a timeline not usually associated with DILI.
>
> Case #2007-05415 (jaundice) appeared to be related to the patient's diagnosis of hepatic cancer. The events improved after the patients hepatic cancer was resected.
>
> Case #2008-03848 (ALT, AST around "3000") in a "hard drinker" reported too little information to make any causality assessment.
>
> The two remaining cases (cases #2007-02194, #2008-00648) were possibly related to the use of silodosin. Case #2007-02194 reported fulminant hepatitis with hepatic encephalopathy and coagulopathy in an 84-year-old male with gastric cancer. The hepatic events occurred 16 days after restarting silodosin postgastric resection surgery. Silodosin was discontinued and the transaminases and bilirubin improved. Case #2008-00648 reported jaundice in a 78-year-old male with chronic hepatitis C 2.5 months after beginning silodosin therapy. Silodosin was discontinued and transaminases and bilirubin improved. Although both cases are confounded by underlying medical conditions (gastric surgery and chronic hepatitis, respectively) both cases reported the events began within 90 days of initiating therapy and gradually improved after dechallenge. Based on the reported timelines a contributory effect from silodosin to the events could not be ruled out.
>
> Therefore, DPV II suggests the following be specified in the product Approval Letter:
> 1. The adverse event terms *jaundice* and —— should be included in the postmarketing adverse events section of the silodosin label.
> 2. To ensure timely evaluation of serious — hepatic events (e.g. jaundice, hepatitis) the sponsor should submit all serious — hepatic events as expedited 15-day Alert Reports.
> 3. The sponsor should obtain comprehensive follow-up of all expedited reports of serious hepatic adverse events.

b(4)

Summary of silodosin effect on liver function tests:

1. Controlled Trials:

a. In U.S. Controlled Phase 3 clinical trials (N=457 on silodosin), a single silodosin subject experienced AST elevation >5X ULN during treatment which normalized despite continuation of silodosin. No subject experienced concomitant elevation of serum transaminase and total bilirubin.
b. In the European Phase 3 study (N=390 on silodosin), no subjects on silodosin experienced transaminase elevation >3X ULN or total bilirubin >2X ULN.
c. In the controlled Japanese database, two silodosin treated subjects in the Phase 2 study (N=182 on silodosin) experienced transaminase elevation >3X ULN without concomitant bilirubin increase during treatment. No silodosin subjects in the Japanese Phase 3 study developed transaminase or bilirubin elevation.

Data from controlled clinical trials do not suggest that silodosin has a clinically meaningful adverse effect on hepatic function.

2. In U.S. open-label extension study, SI04011 (N=661), three silodosin subjects experienced an elevation in AST or ALT >3-5X ULN and a single silodosin subject had an ALT >5X ULN during treatment. In one case, liver function tests returned to normal despite continuation of silodosin. In the three remaining cases, insufficient information was provided to determine causality.

3. There have been seven post-marketing reports of hepatic dysfunction in the setting of silodosin use (see conclusions of consult from Division of Pharmacovigilance II on preceding page).
    a. In two of these cases (2006-04503 and 2007-05415), silodosin was clearly not related to liver dysfunction.
    b. In one case (2008-04048), an assessment of causality is impossible based on the scant information provided.
    c. In the remaining four cases (2006-05221, 2008-00648, 2008-03848, 2008-04048), a relationship to silodosin can not be excluded. One of these cases (2008-00648) satisfies Hy's law criteria. Two of these patients recovered fully and a third had not. In the fourth (2007-02194), the patient had residual hepatic dysfunction, classified as Child-Pugh Class A hepatic cirrhosis.
    d. There have been no deaths from liver failure or patients requiring a liver transplant.

4. Considering data from clinical trials and post-marketing, the evidence is not convincing that silodosin adversely effects hepatic function. However, I do believe that this information should be included in the Post-Marketing Adverse Events section of the label. In addition, the sponsor will be asked to commit to submitting all serious — hepatic events as expedited 15-day Alert Reports and to comprehensively follow-up all expedited reports of serious hepatic adverse events. b(4)

Renal events (elevated creatinine):

The controlled Phase 3 database was searched by the medical officer for subjects whose creatinine shifted from normal at baseline to high on treatment. Fourteen silodosin subjects and eight placebo subjects met this criterion. However, among the fourteen silodosin subjects, five continued in the open-label extension study and their creatinine normalized while still on silodosin. Therefore, a similar number of silodosin patients had shifts from normal to high compared to placebo (9 versus 8).

The magnitude of the shift in serum creatinine was larger for placebo patients compared to silodosin patients (mean of 0.475 mg/dl versus 0.288 mg/dL respectively) when excluding silodosin patient 278013 who had a shift of 3.6 mg/dL. This patient was subsequently found to have renal failure secondary to multiple myeloma.

I agree with the conclusion of the primary medical officer that, based on the available data, silodosin has no meaningful effect on serum creatinine.

Risk of hypotension:

A test for postural hypotension was conducted 2-6 hours following the first dose of study drug in the two Phase 3 controlled trials. Blood pressure and pulse were measured after the patient had been supine for 5 minutes and again at 1 and 3 minutes after standing. The sponsor defined a positive result as follows:

- ≥30 mmHg decrease in SBP
- ≥20 mmHg decrease in DBP or
- ≥20 bpm increase in heart rate.

Study sites were instructed to record an adverse event of "significant change in blood pressure POSTURAL" when these measurement changes occurred in the absence of symptoms. When patients had symptoms during orthostatic tests, the specific symptoms were recorded as an adverse event.

The number and percentage of patients who had a positive test result without symptoms are shown in Table 17.

Table 17. Patients with a positive orthostatic test following drug administration:

Table 7.27 Summary of Positive Orthostatic Results (Sponsor's Criteria) – US Phase 3 Controlled Studies (Safety Population),

Visit 3	Position	Silodosin N=466	Placebo N=457
Post-Dose	1 minute after standing	6 (1.3%)	2 (0.4%)
	3 minutes after standing	9 (1.9%)	2 (0.4%)

Source: NDA 22-206, ser 000, ISS, Table 2.9.1-3

Patients who had positive symptoms during routine orthostatic testing were not included in this summation but were recorded as adverse events.

Orthostatic tests were evaluated by the medical officer using more stringent criteria (ΔSBP$\geq$ -20 mmHg, ΔDBP$\geq$ -20 mmHg or Δ pulse $\geq$20 bpm heart rate), consistent with those used in clinical practice. Results are shown in Table 18.

Table 18. Results of orthostatic blood pressure results using more strict criteria.

Table 7.28 Summary of Positive Orthostatic Results (Strict Criteria) – US Phase 3 Controlled Studies (Safety Population),

Visit	Position	Silodosin N=466	Placebo N=457
Post-Dose	1 minute after standing	7 (1.5%)	4 (0.8%)
	3 minutes after standing	14 (3.0%)	2 (0.4%)

No subject had a systolic blood pressure <90 mmHg during orthostatic testing.

Orthostatic hypotension is an expected side effect of alpha-1-adrenergic antagonists. The incidence of a positive orthostatic test seen in silodosin patients was comparable to that observed in clinical trials of currently marketed alpha-1- adrenergic antagonists. This is a well recognized risk which can be adequately labeled.

Effect of silodosin on the QT interval:

A "thorough QT study" was performed. This was a double-blind, randomized, placebo- and moxifloxacin-controlled, four-arm, parallel study in which 186 healthy male subjects were administered silodosin 8 mg, silodosin 24 mg or placebo once daily for 5 days. Moxifloxacin 400 mg was administered as a single dose on day 5 to establish assay sensitivity. The supra-therapeutic silodosin dose (24 mg) was selected to approximate the "worst-case" scenario exposure (i.e in the setting of concomitant renal disease or use of potent CYP3A4 inhibitors).

The primary endpoint was change from baseline in the time-matched, placebo-corrected QTcI interval for each treatment group. Placebo-corrected, time-matched change from baseline for QTcF was a secondary endpoint.

At all time points measured, the upper bound of the two-sided 90% CI for the baseline-and placebo-corrected QTcI at Day 5 for silodosin 8mg and 24 mg was less than 10 msec. The upper bound of the 99% CI for moxifloxacin was greater than 10 msec at all time points, which confirmed the study's assay sensitivity.

The largest, time-matched, placebo-corrected change from baseline in the upper bound of the 90% CI for QTcF was slightly greater than 10 msec for both the 8 and 24 mg silodosin doses and occurred at hour 6.

QT results are shown in Table 19.

Table 19. Results of the "thorough QT study" (QTcI and QTcF).

Table 7.29 Point Estimates and 90% CIs corresponding to the Largest Upper Bounds for Silodosin (8 mg and 24 mg) and moxifloxacin (sponsor's analyses)

Treatment	Time (hour)	QTcI (ms)	QTcF (ms)
Silodosin 8 mg	6	3.42 (-2.94, 9.78)	4.49(-1.03, 10.01)
Silodosin 24 mg	6	1.39 (-5.03, 7.82)	4.63(-0.95, 10.21)
Moxifloxacin	6	9.59 (-0.36, 19.55)	---

Source: NDA 22-206 ser 000, SI05014 study report, Tables 14.2.1-1, 14.2.1-2, and 11.3.2-1

The IRTQT statistical reviewer performed an independent analysis of the electronically submitted ECG data using QTcF. The ANCOVA model was used to compare the change from baseline between placebo and treatment groups, with treatment as a fixed effect and baseline QTc as covariates. By this analysis, the largest upper bounds of the 2-sided 90% CIs for the mean differences between silodosin and placebo in the time-matched QTcF change from baseline are below 10 ms for both the 8 mg and 24 mg treatment groups (Table 20).

Table 20. Re-analysis of the results of the "thorough QT study" (QTcF)

Table 7.30 Point Estimates and 90% CIs corresponding to the Largest Upper Bounds for Silodosin (8 mg and 24 mg)

Treatment	Time (hour)	ΔΔQTcF and 90%CI (ms)
Silodosin 8 mg	6	3.95 (0.03, 7.87)
Silodosin 24 mg	6	4.80 (0.28, 9.31)
Moxifloxacin	3	9.63 (6.18, 13.09)

Source: IRTQT Consultant Review, dated April 16, 2008

The QT/IRT consultant concluded the following:

> *"No significant effect of silodosin was detected in this "thorough QT" study. The largest upper limits of the two-sided 90% CI for the placebo-corrected mean change in QTcF from baseline between the two doses of silodosin (8 mg and 24mg) and placebo were both below 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline.... Given the lack of dose-response in the primary statistical endpoint and the lack of exposure-response relationship for silodosin, the increase in silodosin exposures due to metabolic inhibition is not expected to prolong the QT interval. "*

There have been no reports during clinical trials or in post-marketing experience of adverse events that may be related to QT prolongation (e.g. seizure, TdP, ventricular tachycardia or sudden death).

I agree with the medical officer and the IRT/QT consultant that there are no data which implicate silodosin with prolongation of the QT interval.

Coadministration of silodosin and PDE5 inhibitors:

In the U.S. controlled Phase 3 trials, use of PDE-5 inhibitors was permitted. Of eleven patients with a positive orthostatic test, one was taking a concomitant PDE-5 inhibitor.

To investigate the effect on blood pressure of concomitant administration of silodosin with a PDE-5 inhibitor, the sponsor conducted a drug interaction study of silodosin with sildenafil, tadalafil, and placebo (SI06002). Twenty-four healthy male subjects aged >45 years, including seven subjects >65 years, were enrolled. Subjects received silodosin 8 mg once daily with breakfast for three consecutive 7-day periods (total of 21 days). At the conclusion of each 7-day period, subjects also received a PDE-5 inhibitor (100 mg sildenafil, 20 mg tadalafil, or placebo) and were monitored for 12 hours. Orthostatic blood pressure tests were performed at 0, 1, 2, 3, 4, 6, 8, and 12 hours after study drug administration.

The maximum mean change from baseline in orthostatic vital signs was similar among the three treatment groups, as shown in Table 21.

Table 21. Mean change from baseline in orthostatic vital signs

Table 7.43. Summary of Maximum Mean Change From Baseline in Orthostatic Vital Signs by treatment group (All Subjects)

Vital sign parameter (upright – supine)	Silodosin + tadalafil (N=22)	Silodosin + sildenafil (N=22)	Silodosin + placebo (N=22)
SBP	-10.2	-5.0	-10.7
DBP	-5.2	-1.6	-2.6
Heart Rate	+14.2	+15.6	+13.9

Source: NDA 22-206 ser 000, SI06002 study report, Table 12.4-1

The greatest number of positive orthostatic tests at any time point were observed in the sildenafil+silodosin group, followed by sildenafil+tadalafil and then silodosin+placebo (Table 22).

Table 22. Number of Positive Orthostatic Tests by Treatment Group

Table 7.44. Number of Positive Orthostatic Test Results by Treatment Group (All Subjects)

Timepoint relative to dosing	Timepoint relative to standing upright	Sildenafil N=22	Tadalafil N=22	Placebo N=22
Pre-dose	1 minute	6 (27.3%)	4 (18.2%)	3 (13.6%)
	3 minutes	1 (4.5%)	3 (13.6%)	2 (9.1%)
Hour 1	1 minute	5 (22.7%)	5 (22.7%)	4 (18.2%)
	3 minutes	5 (22.7%)	6 (27.3%)	2 (9.1%)
Hour 2	1 minute	3 (13.6%)	4 (18.2%)	6 (27.3%)
	3 minutes	4 (18.2%)	4 (18.2%)	3 (13.6%)
Hour 3	1 minute	5 (22.7%)	5 (22.7%)	**7 (31.8%)**
	3 minutes	3 (13.6%)	2 (9.1%)	4 (18.2%)
Hour 4	1 minute	**10 (45.5%)**	**8 (36.4%)**	4 (18.2%)
	3 minutes	4 (18.2%)	6 (27.3%)	1 (4.5%)
Hour 6	1 minute	0	3 (13.6%)	6 (27.3%)
	3 minutes	1 (4.5%)	1 (4.5%)	3 (13.6%)
Hour 8	1 minute	5 (22.7%)	6 (27.3%)	2 (9.1%)
	3 minutes	1 (4.5%)	2 (9.1%)	2 (9.1%)
Hour 12	1 minute	6 (27.3%)	4 (18.2%)	5 (22.7%)
	3 minutes	5 (22.7%)	3 (13.6%)	4 (18.2%)
	Total	59	67	58

No subject in any dose group had an SBP less than 90 mmHg or pulse greater than 100 bpm at any time point in the 12 hour period following combination dosing.

There was no significant difference in the incidence of adverse events among the three treatment groups.

The medical officer concluded the following:

- The population studied was generally healthy and may not be representative of the patients likely to be prescribed a PDE-5 inhibitor in clinical practice (e.g. diabetics, pre-existing cardiovascular disease). Any synergistic effect of silodosin and a PDE-5 inhibitor on blood pressure may be enhanced in patients with co-morbidities on multiple medications.

- Although the maximum mean change in orthostatic vital sign parameters was similar among the three combination treatment groups, the number of positive orthostatic tests was greater when silodosin was combined with a PDE-5 inhibitor than with placebo. This was true both for subjects 45-64 years of age and those >65 years.

- This study's small sample size limits the conclusions that can be drawn regarding the safety of silodosin combined with PDE-5 inhibitors, particularly in patients >65 years (N=6).

- At the pre-NDA meeting held on April 10, 2007, DRUP advised the sponsor that "PDE5 inhibitor class labeling currently exists for concomitant use with all alpha blockers based on a large body of evidence from controlled clinical trials. [redacted] b(4)

- This small study does not support [redacted] b(4)

I agree with the medical officer's conclusions and recommendations.

Safety summary:

I agree with the following conclusions reached by the primary medical officer.

- Retrograde ejaculation was the most frequently reported adverse event and occurred in over 30% of silodosin-treated subjects in U.S. Phase 2/3 clinical trials.
- Other common adverse events were diarrhea, dizziness, nasopharyngitis and orthostatic hypotension.
- All common adverse events observed in silodosin clinical trials are consistent with the side effect profile of approved alpha-1-adrenergic antagonist drugs.
- Silodosin therapy is associated with a mean decrease in systolic and diastolic blood pressure of 1.1 and 0.5 mmHg, respectively, compared to placebo following up to 12 weeks of treatment. Pulse increased by 0.7 bpm over placebo. These changes in vital signs are not considered to be clinically significant.
- QT testing is adequate. There is no evidence to date to suggest that silodosin has a significant effect on the QT interval.
- Silodosin was not associated with any significant change in laboratory parameters.
- The majority of serious adverse events reported during post-marketing for silodosin were related to vasodilatory side effects (e.g. syncope, orthostatic hypotension) that are typical for members of the alpha-1- adrenergic antagonist class of drugs, are well recognized, and can be adequately labeled.
- There have been seven post-marketing reports of significant liver dysfunction in patients treated with silodosin. None are clearly related to silodosin treatment. There was no signal in controlled clinical trials of silodosin causing an increase in hepatocellular enzymes or otherwise adversely affecting liver function.

In U.S. controlled Phase 2/3 trials, there was a single serious adverse event that is likely to be related to silodosin – a case of syncope (Patient 272046). This case was complicated by the fact that the patient was also receiving the excluded medication prazosin (another alpha-1-adrenergic antagonist).

Intra-operative floppy iris syndrome (IFIS) was observed in one patient in the open-label safety extension trial. IFIS is currently listed as a precaution in labels of all members of the α-1-antagonist class of drugs and information concerning IFIS will be included in silodosin labeling.

The most common post-marketing serious adverse event reports received involving silodosin have been related to vasodilatory side effects (e.g. loss of consciousness, syncope). Other notable post-marketing serious adverse event reports have been seven cases of hepatic dysfunction, none of which can be clearly related to silodosin. These serious adverse events should be included in the [redacted] of the product label and the sponsor will be asked to commit to submitting post-marketing serious liver adverse events as expedited 15 day reports. b(4)

9. Advisory Committee Meeting

Silodosin is the fifth alpha-adrenergic antagonist to be approved for the treatment of benign prostatic hyperplasia. It is a new molecular entity, but the efficacy appears to be comparable to the other approved drugs in its class and no new safety concerns were identified. No advisory committee was convened.

10. **Pediatrics** b(5)

[redacted]

- NDA 22-206, Rapaflo (silodosin), was studied for BPH. The studies were submitted on December 13, 2007, and the PDUFA Goal Date is October 13, 2008.
- The Division is recommending a full waiver because studies are impossible or highly impractical because the disease does not exist in children.

[redacted] b(5)

11. Other Relevant Regulatory Issues

a. Division of Scientific Investigations:

DSI inspected four clinical sites where patients were enrolled into the two pivotal United States Phase 3 trials (studies 4009 and 4010). The sites were selected for inspection because they enrolled the largest numbers of subjects. In addition, the sponsor site, Watson Laboratories, was inspected because silodosin is a new molecular entity.

The DSI inspector concluded in his memorandum that "there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol. No underreporting of adverse events was noted. Overall, data generated for protocols SI04009 and SI04010 at these clinical sites appear acceptable for use in support of NDA 22-206."

b. **Division of Medication Errors and Prevention:**

In a memorandum dated June 3, 2008, DMEP expressed no objection to the use of the proprietary name, Rapaflo, for this product.

c. Study Endpoints and Label Development Team (SEALD):

A consultation from SEALD regarding the label (in Physician's Labeling Rule format) was obtained and recommended changes were incorporated into labeling.

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

A consultation from DDMAC regarding the label was obtained and recommended changes incorporated into labeling.

e. **Division of Pharmacovigilance II (DPV II):**

The DPV II was consulted to review the post-marketing hepatic serious adverse event reports involving silodosin. The DPV II concluded that of the six cases they reviewed (a seventh was received after the consult request was made and was not reviewed), two were possibly related to use of silodosin. Therefore, DPV II suggests the following be specified in the product Approval Letter:

1) "The adverse event terms *jaundice* and — should be included in the postmarketing adverse events section of the silodosin label. b(4)
2) To ensure timely evaluation of serious — iepatic events (e.g. jaundice, hepatitis) the sponsor should submit all serious — . hepatic events as expedited 15-day Alert Reports.
3) The sponsor should obtain comprehensive follow-up of all expedited reports of serious hepatic adverse events."

f. The Interdisciplinary Review Team for QT Studies (IRT-QT):

The IRT-QT was consulted regarding the "thorough QT study." The consultation is discussed under the Safety section of this memorandum.

g. Financial Disclosure:

Financial disclosure was made for all required studies submitted to the NDA. There is no evidence to suggest that a financial relationship had any impact on the study results.

There are no other unresolved regulatory issues.

12. **Labeling**

Labeling negotiations with the sponsor were concluded on September 26, 2008. In addition to labeling, the sponsor committed to providing 15-day expedited reports for post-marketing liver serious adverse events.

13. Recommendation/Risk Benefit Assessment

I agree with the recommendation of the primary medical officer, clinical pharmacology reviewer, pharmacology/toxicology reviewer, CMC reviewer, and statistical reviewer that NDA 22-206 (silodosin for the treatment of the signs and symptoms of benign prostatic hyperplasia) be approved.

Efficacy using accepted endpoints (IPSS and Q_{max}) was demonstrated in two adequate, controlled phase 3 studies. Although no comparative studies have been performed, the treatment effect appears similar to that of the four approved drugs in this class (alpha-1- adrenergic antagonists) for the treatment of benign prostatic hyperplasia.

No new safety concerns have been identified. Like other alpha blockers, the most significant risk is hypotension. This adverse event is well recognized with this class of drugs and will be labeled under WARNINGS and PRECAUTIONS.

DPV II suggests the following be specified in the product Approval Letter:

- To ensure timely evaluation of serious hepatic events (e.g. jaundice, hepatitis) the sponsor should submit all serious hepatic events as expedited 15-day Alert Reports.
- The sponsor should obtain comprehensive follow-up of all expedited reports of serious hepatic adverse events."

b(4)

The sponsor has agreed with the above DPV II recommendations and the commitment to report serious liver adverse events as expedited 15-day Alert Reports will be included in the action letter.

No Post-Marketing commitments are necessary.

At the time of writing this memorandum, the inspection report for a manufacturing facility has not been received. (see Addendum dated October 8, 2008, below). There are no other outstanding issues regarding this NDA submission.

Addendum (October 8, 2008):

The following CMC memorandum was received on October 7, 2008.

"At the time the CMC review was written, the Establishment Evaluation was pending. On October 7, 2008, the Office of Compliance gave an overall acceptable recommendation for the manufacturing facilities. Thus, this application is recommended for approval from the perspective of Chemistry, Manufacturing, and Controls. This memorandum closes all pending issues for this NDA from the CMC perspective."

The CMC memorandum closes out the only previously pending review. There are no issues regarding this NDA submission which have not been resolved.

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
10/8/2008 08:43:25 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-206
Letter Date	December 11, 2007
PDUFA Goal Date	October 11, 2008
Reviewer Name	Olivia Easley, MD
Review Completion Date	August 27, 2008
Established Name	silodosin
(Proposed) Trade Name	Rapaflo™
Therapeutic Class	alpha-1 adrenergic antagonist
Applicant	Watson Laboratories, Inc.
Formulation	4 mg and 8 mg capsules
Dosing Regimen	8 mg orally once daily
Indication	treatment of signs and symptoms of benign prostatic hyperplasia (BPH)
Intended Population	adult men

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1. Executive Summary

1.1 Recommendation on Regulatory Action

This reviewer recommends, from a clinical perspective, that silodosin 8 mg tablets taken once daily (qd) with food for the indication of "treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)", be **approved** pending satisfactory inspection by the Office of Compliance of the Japanese manufacturing facilities (see addendum, page 81). Efficacy of silodosin, as assessed by change from baseline to week 12 in total score of the International Prostatic Symptom Score (IPSS), was demonstrated in one U.S. controlled Phase 2 trial and two U.S. controlled Phase 3 trials. Silodosin has an acceptable safety profile that is consistent with other members of the α-1-antagonist drug class.

Labeling changes are recommended to contraindicate co-administration of silodosin with potent CYP3A4 inhibitors and to reduce the dose of silodosin to 4 mg once daily in patients with moderate renal impairment.

1.2 Recommendation on Post-marketing Actions

Based on the seven foreign post-marketing serious adverse event reports of hepatic dysfunction (see section 7.1.8), the approval letter should include a request that the sponsor continue to submit reports of hepatotoxicity with serious outcomes as expedited (15-day) alerts and to provide follow-up on these reports.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Silodosin is a selective α-1-adrenergic receptor antagonist developed for the treatment of the signs and symptoms of BPH (sometimes referred to as lower urinary tract symptoms, or LUTS). There are currently four selective α-1- adrenergic antagonists approved by the FDA for the treatment of BPH (terazosin, doxazosin, tamsulosin, and alfuzosin).

Silodosin 4 mg bid was approved for the BPH indication in Japan in January, 2006. The product is currently in Phase 3 development in the European Union under Recordati, S.p.A. b(4)

In support of NDA 22-206, the sponsor submitted one placebo-controlled Phase 2 trial and 2 pivotal Phase 3 studies, all conducted in the U.S. The Phase 2 study included two silodosin doses – 4 mg and 8 mg once daily – and involved eight weeks of active treatment. The study design of the Phase 3 trials, in which subjects received silodosin 8 mg or placebo once daily for 12 weeks, was identical. The primary endpoint in all studies was change from baseline to endpoint/last observation carried forward (LOCF) in total IPSS. Maximum urinary flow rate (Qmax) was a co-primary endpoint in the Phase 2 trial and a pre-specified secondary endpoint in the two Phase 3 studies.

A total of 1,187 patients (566 on silodosin 8 mg once daily; 88 on silodosin 4 mg once daily) with BPH were studied in U.S. controlled Phase 2/3 trials. Duration of drug exposure ranged from 8 weeks in the Phase 2 trial to 12 weeks in the two Phase 3 studies. Of these 1,187 patients, 661 continued into a 9-month open-label safety study of silodosin 8 mg once daily.

1.3.2 Efficacy

The primary efficacy endpoint in the U.S. controlled Phase 2 trial and the two U.S. pivotal Phase 3 trials was change from baseline to endpoint/LOCF in total IPSS (also known as the American Urologic Association Symptom Score). The IPSS (or AUA-SS) is a questionnaire currently used as a primary endpoint for all drug trials of the treatment of BPH. Change from baseline to LOCF in Q_{max} was a co-primary endpoint in the Phase 2 study and a pre-specified important secondary endpoint in both Phase 3 trials.

The main efficacy conclusions from the U.S. controlled Phase 2/3 trials are as follows:

- Silodosin 8 mg once daily results in a placebo-subtracted mean 2.8 point decrease in total IPSS ($p<0.001$) from baseline to endpoint (last observation carried forward).
- Silodosin 8 mg once daily also results in a placebo-subtracted mean increase in Qmax of 1.1 ml/sec ($p=0.0002$) from baseline to endpoint (LOCF).

Efficacy results from each individual trial are shown in Table 1.1

Table 1.1 Placebo-subtracted mean change from baseline to endpoint/LOCF in IPSS and Qmax, U.S. controlled Phase 2/3 trials

	KMD-3213-US012-99 (N=90)	SI04009 (N=233)	SI04010 (N=233)
ΔIPSS	-2.8	-2.9	-2.9
p-value	0.0018	<0.001	<0.001
ΔQmax	+1.9	+1.0	+1.0
p-value	0.0174	0.0060	0.0431

Reviewer's comment: For comparison, effect on total IPSS and Qmax of two currently marketed α-1-antagonists indicated for BPH is shown in Table 1.2.

Table 1.2 placebo-subtracted mean Change from baseline in total IPSS and Qmax for comparator drugs

Drug/dose	Placebo-subtracted Δ total IPSS (baseline to week 12)	Placebo-subtracted Δ Qmax (baseline to week 12)
Alfuzosin 10 mg	-2.0	+1.0 ml/sec
Tamsulosin 0.4 mg	-2.1	+0.4 ml/sec

Source: approved labels for alfuzosin (Uroxatral®) and tamsulosin (Flomax® dated 3/29/07 and 2/16/07, respectively.

1.3.2 Safety

Safety data are drawn from a total of twenty-five clinical studies performed with silodosin in 1,774 subjects (1,371 on silodosin).

Twenty-one clinical pharmacology studies in 634 subjects (474 on silodosin, 113 on placebo, and 47 on moxifloxacin) have been performed with silodosin to characterize its pharmacokinetics and pharmacodynamics. Doses of silodosin ranged from 0.1 to 48 mg given for 1 to 21 days. These trials were conducted in Japan, Europe and the U.S.

Three controlled Phase 2/3 studies have been conducted with silodosin in the US in 1,187 patients with BPH. Phase 2 study **KMD 3213-US021-99** enrolled 264 patients (N=90 on 8 mg silodosin qd; N=88 on 4 mg qd). Phase 3 studies **SI04009** and **SI04010** enrolled 461 and 462 patients, respectively (N=466 on silodosin 8 mg qd). In addition, of the 1,187 patients enrolled in these trials, 661 patients continued into a 9-month open-label safety study (**SI04011**) of silodosin 8 mg qd. In sum, a total of 897 patients were exposed to daily doses of 8 mg silodosin in the four US Phase 2/3 studies.

Additional safety data in 1,858 patients (901 on silodosin) come from six Japanese Phase 2/3 studies and a single European Phase 3 study, the designs of which are shown in Table 1.3.

Table 1.3 Summary Descriptions of Japanese and European Phase 2/3 Studies

Study	Sample Size and Dose Groups	Design	Duration of Study Drug Treatment
Japanese Phase 2/3 Trials			
KMD 3213-201	N=141 BPH patients 47 on 0.2 mg silodosin 49 on 2 mg silodosin 45 on 4 mg silodosin	Open-label, parallel	28 days
KMD 3213-202	N=271 BPH patients 90 on silodosin 4 mg 92 on silodosin 8 mg 89 on placebo	Double-blind (DB) parallel, placebo-controlled	4 weeks
KMD 3213-203	N=108 BPH patients 38 on silodosin 4 mg 37 on silodosin 8 mg 33 on placebo	Open-label, parallel, safety extension of KMD-202	52 weeks
KMD 3213-206	N=12 BPH patients 12 silodosin 8 mg	Open-label	4 weeks
KMD-3213-303	N=457 BPH patients 176 on silodosin 8 mg 192 on tamsulosin 89 on placebo	DB, placebo-controlled	13 weeks
KMD-3213-305	N=364 BPH patients 364 on silodosin 8 mg	Open-label safety extension of KMD-303	52 weeks
European Phase 3			
KMD3213-IT-CL-0245	N=977 390 on silodosin 8 mg 393 on tamsulosin 0.4 mg 194 on placebo	DB, placebo-controlled	12 weeks

Source: NDA 22-206 ser 000, section 2.7.4, Table A-1.

Treatment emergent adverse events reported during clinical trials were consistent with known side effects of α-1-antagonists. The most frequently reported adverse events in the two U.S. Phase 3 trials are shown in Table 1.4.

Table 1.4 Treatment-emergency adverse events occurring in >2% of silodosin patients, U.S. Controlled Phase 3 trials

Adverse Event	Silodosin N=466 n (%)	Placebo N= 457 n (%)
Retrograde ejaculation	131 (28.1)	4 (0.9)
Dizziness	15 (3.2)	5 (1.1)
Diarrhea	12 (2.6)	6 (1.3)
Orthostatic hypotension	12 (2.6)	7 (1.5)
Headache	11 (2.4)	4 (0.9)
Nasopharyngitis	11 (2.4)	10 (2.2)
Nasal congestion	10 (2.1)	1 (0.2)

Source: NDA 22-206 ser 000, Table 2.5.4

In U.S. controlled Phase 2/3 trials, there was a single serious adverse event that is likely to be related to silodosin – a case of syncope (Patient 272046). This case was complicated by the fact that the patient was also receiving the excluded medication, prazosin – another α-1-antagonist.

Intra-operative floppy iris syndrome (IFIS) was observed in one patient in the open-label safety extension trial, **SI04011** (Patient 129003). IFIS is currently listed as a precaution in labels of all members of the α-1-antagonist class of drugs.

The most common post-marketing serious adverse event reports received involving silodosin have been related to vasodilatory side effects (e.g. loss of consciousness, syncope). Other notable post-marketing serious adverse event reports have been seven cases of hepatic dysfunction, none of which can be clearly related to silodosin. These serious adverse events should be included in the [redacted] section of the product label. b(4)

1.3.4 Dosing Regimen and Administration

The 8 mg once daily dose of silodosin with food was selected based on safety and tolerability information from Phase 1 investigations and the US Phase 2 efficacy and safety data. Dose rationale is summarized below:

- The long terminal elimination half-life of silodosin and the extended pharmacokinetic profile of silodosin's active metabolite KMD-3213G provided the rationale for once a day dosing
- A small reduction in C_{max} (~30%), an increase in t_{max} (approximately 45 minutes), with minimal effects on AUC when silodosin is taken with meals supported dosing with meals.
- More robust efficacy of the 8 mg dose over the 4 mg dose on change in total IPSS and Q_{max} in the controlled U.S. Phase 2 trial, as in Table 1.5.

Table 1.5 Placebo-Subtracted Mean Change from baseline to week 8/LOCF in co-primary endpoints, total AUA-SS and Q_{max}, US Phase 2 study, KMD3213-US021-99

Primary Efficacy Variable	8 mg silodosin N=90	4 mg silodosin N=88
IPSS total score	-2.8	-1.6
p-value (vs. placebo)	0.0018	0.0355
Q_{max}	+1.9	+1.4
p-value (vs. placebo)	0.0174	0.0966

Source: NDA 22-206 ser 000, KMD3213-US021-99 study report, Tables 5.1 and 5.2

Reviewer's comment: This reviewer agrees with the selection of 8 mg once daily as the therapeutic dose.

1.3.5 Drug-Drug Interactions

Systemic exposure to silodosin increases when co-administered with ketoconazole, a potent CYP3A4 inhibitor that also inhibits P-glycoprotein (P-gp). Exposure multiples are shown in Table 1.6.

Table 1.6 Exposure multiple for silodosin AUC and Cmax following co-administration with potent CYP3A4 inhibitor, ketoconazole

	AUC	C_{max}
Silodosin + ketoconazole[1]	↑3.26	↑3.66
Silodosin + ketoconazole[2]	↑3.1	↑3.7

[1] Study KMD-306-UK, silodosin 4 mg alone, and in combination with ketoconazole 200 mg qd, n=16 healthy males

[2] Study SI06008, silodosin 8 mg alone, and in combination with ketoconazole 400 mg qd, n= 22 healthy males

The sponsor has recommended that [redacted] b(4)

Reviewer's comment: This reviewer believes that potent CYP3A4 inhibitors should be contraindicated in patients taking silodosin. [redacted] b(4)

The DRUP clinical pharmacology reviewer agrees with this reviewer's recommendation.

1.3.6 Special Populations

Gender: Silodosin is contraindicated in women.

Race: No clinical pharmacology investigations of the effects of race have been performed. In U.S. Phase 2/3 studies, no overall differences in safety or efficacy were

observed for patients of different races. However, the sample size of non-Caucasians was relatively small (N=86) which limits interpretation of the safety data.

Age: The pharmacokinetics and safety of a single dose of silodosin were evaluated in 12 males aged >65 years, and 9 males aged 20 to 35 years (study KMD-105). Silodosin AUC increased by 15% in elderly subjects, but there was no change in Cmax.

Of the 897 patients exposed to silodosin in the four US Phase 2/3 trials, 384 were older than 65 years and 96 were older than 75 years. The adverse event of orthostatic hypotension was slightly more common among subjects >75 years (5.2% versus 2.9% in subjects <65 years). Otherwise there were no overall differences in safety observed between elderly patients and younger patients. This information should be included in the _____ section of the label, but no dose adjustment is recommended in the elderly. b(4)

No overall difference in efficacy was observed between older and younger adult patients.

Silodosin has not been studied in children and is currently contraindicated in the pediatric population.

Renal Insufficiency: Silodosin C_{max} and AUC values were approximately 3-fold higher in patients with moderate renal impairment [Creatinine Clearance (CCr) 30-50 ml/min] compared to subjects with normal renal function.

In the four US Phase 2/3 clinical trials, an increased incidence of dizziness and orthostatic hypotension was observed in patients with moderate renal impairment compared to subjects with normal renal function (Ccr>80 ml/min) or only mild impairment (50-80 ml/min) (Table 1.7).

Table 1.7 Most Common Treatment Emergent Adverse Events by Baseline Renal Function, US Phase 2/3 Trials

Adverse Event – Preferred Term	Normal Renal Function N=620	Mild Renal Impairment N=245	Moderate Renal Impairment N=21
Retrograde ejaculation	213 (34.4%)	66 (26.9%)	5 (23.8%)
Dizziness	23 (3.7%)	8 (3.3%)	**3 (14.3%)**
Orthostatic hypotension	20 (3.2%)	6 (2.4%)	**2 (9.5%)**
Source: NDA 22-206 ser 000, ISS, Table 2.2.4-1, Parts 1.1, 2.2 and 3.1			

Reviewer's comments: Based on these data this reviewer recommends that the dose of silodosin be reduced to 4 mg once daily in patients with moderate renal impairment (CCr 30-50 ml/min). No dose adjustment is recommended for patients with mild renal impairment.

As there are no data on the use of silodosin in patients with severe renal insufficiency, the drug should not be used in this population.

The DRUP clinical pharmacology reviewer agrees with these recommendations.

Additional discussion of dosing in special populations is found in section 8.3 of this review.

Hepatic Insufficiency: Silodosin exposure decreased slightly in subjects with moderate liver dysfunction (Child-Pugh score 7-9) compared to age and weight-matched controls (AUC decreased by 26%, C_{max} by 26-37%). No dose adjustment is recommended in subjects with mild or moderate hepatic impairment.

Silodosin has not been studied in patients with severe hepatic impairment (Child-Pugh score $\geq$10) and therefore its use is not recommended in this population.

Reviewer's comments: The DRUP clinical pharmacology reviewer agrees with these recommendations.

2 Introduction and Background

2.1 Product Information

Silodosin (proposed trade name **RAPAFLO™)** is a selective α-1-adrenergic antagonist. The proposed indication is the "treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)." The recommended dose is 8 mg orally with food once daily.

Silodosin (Urief®) was approved in Japan on January 23, 2006, for the treatment of "bladder outlet obstruction associated with BPH." The usual recommended dose of Urief® is 8 mg daily in two divided doses, after breakfast and dinner. The market authorization holder (MAH) for silodosin in Japan is Kissei Pharmaceutical Co., Ltd.

Silodosin is also being developed for the treatment of BPH in Europe [redacted] by Recordati, S.p.A. [redacted] b(4)

[redacted]

2.2 Currently Available Treatment for Indication

Treatment of the signs and symptoms of BPH includes pharmacologic therapy [5-alpha reductase inhibitors and α-1-adrenergic antagonists, either alone or in combination], minimally invasive procedures [e.g. trans-urethral needle ablation of the prostate (TUNA)] and surgery [primarily transurethral resection of the prostate (TURP)].[1]

[1] Burnett, A.L. and A.J. Wein. Benign Prostatic Hyperplasia in Primary Care: What You Need to Know. *J Urol* 2006 Mar; 175: S19-S24.

Alpha-1-adrenergic antagonists are believed to improve the symptoms of BPH by relaxing the prostatic and bladder neck smooth muscle which reduces the degree of bladder outlet obstruction. There are four selective α-1-adrenergic antagonists currently approved in the U.S. for the treatment of BPH – terazosin (Hytrin®), doxazosin (Cardura®), tamsulosin (Flomax®), and alfuzosin (Uroxatral®).

2.3 Availability of Proposed Active Ingredient in the United States

Silodosin is not approved for any indication in the United States.

2.4 Important Issues with Pharmacologically Related Products

There are currently three identified α-1-receptor subtypes (α1A, α1b and α1d). All three subtypes exist in a wide range of human tissues, including the systemic vasculature, the prostatic smooth muscle and bladder neck. The α1A subtype is believed to play a primary role in mediating prostatic smooth muscle contraction.[2]

The most significant safety concern with the selective α-1-antagonists is the occurrence of "vasodilatory" symptoms, such as dizziness, orthostatic hypotension and syncope that result from these drugs' activity on α -1 adrenergic receptors in the systemic vasculature. Theoretically, drugs that are pharmacologically "uroselective" – binding α-1A receptors preferentially over α-1b or α-1d – will have fewer vasodilatory effects.

2.5 Presubmission Regulatory Activity

Significant presubmission regulatory activity is shown in Table 2.1.

[2] Kaplan, S. A. alpha-blocker Therapy: Current Update. *Rev Urol.* 2005; 7 Suppl 8: S34-42.

Table 2.1 Presubmission Regulatory Activity, NDA 22-206		
Date	Activity	Comments from FDA
August 13, 1998	IND opened for BPH indication	
July 3, 2003	FDA Clinical review comments regarding Phase 3 clinical plans	An EOP2 meeting would be necessary to discuss dose selection for Phase 3 clinical development
February 10, 2005	EOP2 meeting	Determination that no preclinical issues were outstanding and that data support initiation of Phase 2 Recommended lower dose of silodosin for special population
May 2, 2005	FDA Phase 3 clinical protocol review comments	Investigation of only one dose (8 mg) requires additional discussion Suggestion that serum prolactin data be obtained
May 23, 2005	Corrections to the EOP2 meeting minutes	As a result of additional discussions, consensus of testing only one dose (8 mg) in Phase 3 was reached, with the risks of this approach outlined.
July 22, 2005	Clinical guidance teleconference	Suggestions for prolactin and thyroid monitoring provided
August 12, 1005	Clinical guidance teleconference	Agreement for not including thyroid ultrasound and an age-matched control group as part of thyroid monitoring during Phase 3
January 5, 2006	Watson telephone contact report	A reduction in sample size for the Phase 3 studies was acceptable to the Division
December 1, 2006	FDA clinical review comments on the thorough QTc study	Multiple suggestions to the thorough QTc study design were provided
January 19, 2007	FDA clinical review comments for the statistical analysis plans for the Phase 3 protocols	Division commented that they consider the primary endpoint for the Phase 3 studies to be the IPSS and not the IPSS-1 (IPSS-1 includes an eighth quality of life question).
March 16, 2007	FDA clinical review comments for the SAPs for the Phase 3 protocols	Division agreed that the SAPs for the Phase 3 studies were acceptable.
March 29, 2007	Clinical guidance teleconference regarding design of thorough QT study	Supratherapeutic dose of 24 mg was recommended for the thorough QTc study The Division recommended a lower therapeutic dose (4 mg) for use in special populations based on pharmacokinetic data
July 23, 2007	Pre-NDA meeting	Agreement to supply available European safety data at time of filing without integration into U.S. safety database Agreement on the filing of a pediatric — with the NDA.

b(4)

Source: NDA 22-206 ser 000, Table 2.5-1 in Clinical Overview

3. Significant Findings from Other Review Disciplines

3.1 CMC

The following is a summary of the Chemistry Assessments according to the DRUP CMC review:

Drug Substance

The drug substance is silodosin. Detailed information related to the drug substance is found in DMF # [redacted] The DMF has been reviewed and found to be adequate. b(4)

Drug Product

The drug product is a white, opaque, hard gelatin capsule, and is available in two strengths – 4 mg and 8 mg. The capsules are manufactured by [redacted] b(4) The identity, purity, strength, and quality of the drug product are ensured by the implemented in-process controls and drug product specification.

The formulation composition and manufacturing process for the to-be-marketed 4 mg capsules will be the same as that used in the Phase III clinical trials. Two 4-mg capsules were used in the Phase III clinical trials to deliver 8 mg of Silodosin. The to-be-marketed 8 mg capsules will be proportionally filled with the same [redacted] used in the 4 mg capsules. The dissolution profiles of the 8 mg capsules and two 4 mg capsules are similar. b(4)

The proposed expiration date of 24 months for the capsules (4 mg and 8 mg) is supported by the stability data.

According to the DRUP CMC reviewer, "this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance and drug product. Therefore, from a CMC perspective, this NDA is recommended for 'Approval' with pending review on labels, and Establishment Evaluation."

Reviewer's comment: At the time of this review, the inspection of the Japanese manufacturing site by the FDA Office of Compliance is pending.

3.2 Pharmacology/Toxicology

The DRUP pharmacology/toxicology reviewer has identified the following non-clinical safety issues as relevant to clinical use:

- **Thyroid Follicular Cell Tumors in Rats**

In a 2-year oral carcinogenicity study in rats, an increased incidence of thyroid follicular cell tumors was seen in male rats receiving doses of 150 mg/kg [approximately 8 times the exposure of the maximum recommended human dose (MHRE) via comparative

silodosin AUC]. In addition, silodosin induced stimulation of TSH secretion in the male rat and decreased circulating levels of thyroxine (T4).

However, according to the pharmacology/toxicology team leader, "these tumors were related to increased UDP-GT levels, a common finding specific to rodents."

Reviewer's comment: In Phase 3 clinical trials, thyroid physical examination and measurement of serum thyroid function tests (free and total T4, TSH, T3) was performed at screening and end of treatment. Thyroid function tests were also monitored during the open-label extension study (SI04011). There was no evidence of an effect of silodosin on thyroid hormones in up to 40 weeks of observation or on thyroid physical examination.

- **Increased incidence of Mammary Gland Adenocanthoma and Adenocarcinomas in Female Mice**

In a 2-year oral carcinogenicity study in mice administered doses up to 200 mg/kg/day in males and 400 mg/kg/day in females, there were no significant tumor findings in male mice. Female mice treated for 2 years with doses of 150 mg/kg/day or greater (approximately 29 times the MRHE via AUC) had statistically significant increases in the incidence of mammary gland adenoacanthoma and adenocarcinomas ($p < 0.001$). The increased incidence of mammary gland neoplasms in female mice was considered secondary to silodosin-induced hyperprolactinemia.

The DRUP pharmacology/toxicology reviewer notes that, clinically, these findings in mice are not considered relevant because:

1) the drug is not indicated in females
2) there is a sufficient safety margin between the dose at which tumors occurred and the clinical dose
3) induction of mammary adenomas and carcinomas has been noted in mice following administration of other drugs of this class without clinical findings in adult male humans.

Reviewer's comment: In the two U.S. Phase 3 clinical trials, serum prolactin levels were measured at baseline and week 12/ET. No increase in serum prolactin levels was observed. In addition, breast examination was performed and there was no increase in breast examination abnormalities among silodosin-treated patients.

- **Effects on male rat fertility**

Treatment of male rats with silodosin for 15 days resulted in decreased fertility at the high dose of 20 mg/kg/day (approximately 2 times the MRHE) which was reversible following a two week recovery period. No effect was observed at 6 mg/kg/day.

Reviewer's comment: According to the DRUP pharmacology/toxicology reviewer, the effects on male rat fertility are believed to be a class effect of alpha-1-antagonist drugs and have been reported in pre-clinical studies of currently marketed alpha-1-antagonists. It is not known if the effect is species-specific and if these findings have any clinical

relevance. This information should be included in the product label with a statement that clinical relevance is unknown. It is reassuring, however, that these effects were reversible.

3.3 Clinical Pharmacology

The DRUP clinical pharmacology review team has concluded that NDA 22-206 is "acceptable from a Clinical Pharmacology perspective, provided the labeling comments are adequately addressed." The reviewer's labeling recommendations are summarized below:

1. Silodosin should not be used in patients with severe renal impairment. The dose should be lowered to 4 mg once daily in patients with moderate renal impairment. No dosage adjustment is needed in patients with mild renal impairment.
2. No dosage adjustment is needed in patients with mild and moderate hepatic impairment. No data are available in patients with severe hepatic impairment. Patients should be alerted to report adverse events such as dizziness, light headedness, and fainting episodes.
3. No dosage adjustment is needed for age.
4. The effect of a high fat, high calorie meal on the pharmacokinetics (PK) of silodosin was not evaluated. A moderate fat, moderate calorie meal decreased silodosin C_{max} by 18 – 43% and decreased AUC by 4.3 - 49% (across 3 different studies). Patients should be advised to take silodosin with food in order to reduce the risk of adverse events such as orthostatic hypotension.
5. CYP3A4 inhibitors: Silodosin should not be used in patients taking strong inhibitors of CYP3A4. Caution should be exercised when co-administering silodosin with moderate CYP3A4 inhibitors.
6. P-glycoprotein (P-gp) inhibitors: *In vitro* studies indicated that silodosin is a P-gp substrate. A drug interaction study with a strong P-gp inhibitor such as cyclosporine or itraconazole has not been conducted. A drug interaction study with ketoconazole, a CYP3A4 inhibitor that may also inhibit P-gp, showed significant increase in exposure to silodosin. Silodosin should not be used concomitantly with strong P-gp inhibitors (e.g. cyclosporine or itraconazole).
7. Silodosin is partly metabolized via the UGT2B7 pathway. Co-administration with inhibitors of UGT2B7 (e.g., probenacid, valproic acid, fluconazole) may potentially increase exposure to silodosin.
8. Co-administration of silodosin did not significantly affect the PK of digoxin, a P-gp substrate with narrow therapeutic index.
9. *In vitro* studies indicated that silodosin administration is not likely to inhibit the activity of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 or induce the activity of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4, and P-gp.

Reviewer's comments: The clinical reviewer agrees with the clinical pharmacology team's labeling recommendations.

3.4 Biostatistics

No significant problems were identified in the statistical review that would affect approvability of this application.

3.5 Consults from Other Divisions

3.5.1 Division of Medication Errors and Prevention (DMEP)

In a memorandum dated June 3, 2008, DMEP expressed no objection to the use of the proprietary name, Rapaflo, for this product.

DMEP recommended changes to the labels on the drug container, package and —— —— to reduce the risk of medication errors. Their recommendations, which related to the type of font and the position of the drug name on the labels and containers, were sent to the sponsor on June 23, 2008.

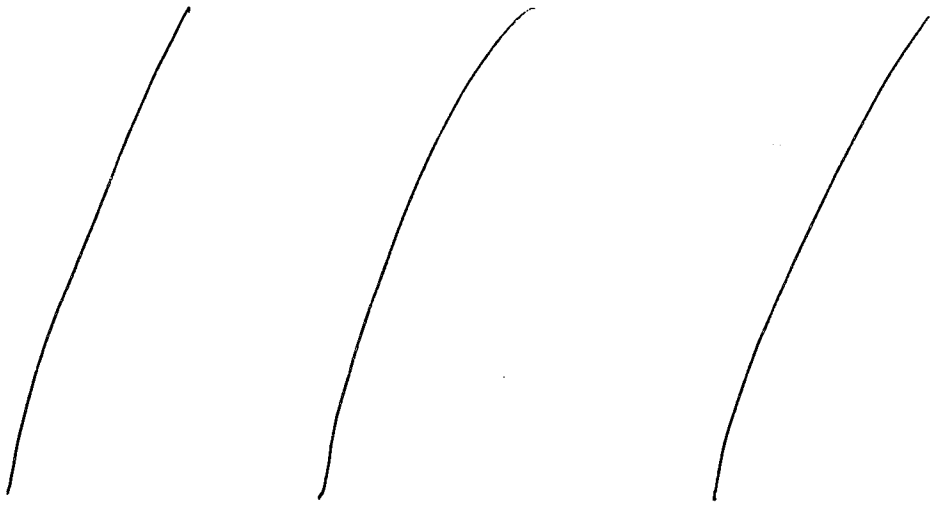
b(4)

3.5.2 Study Endpoints and Label Development Team (SEALD)

The proposed package insert was reviewed by SEALD. Changes recommended by SEALD were made so that the label is in compliance with the physician's labeling rule format.

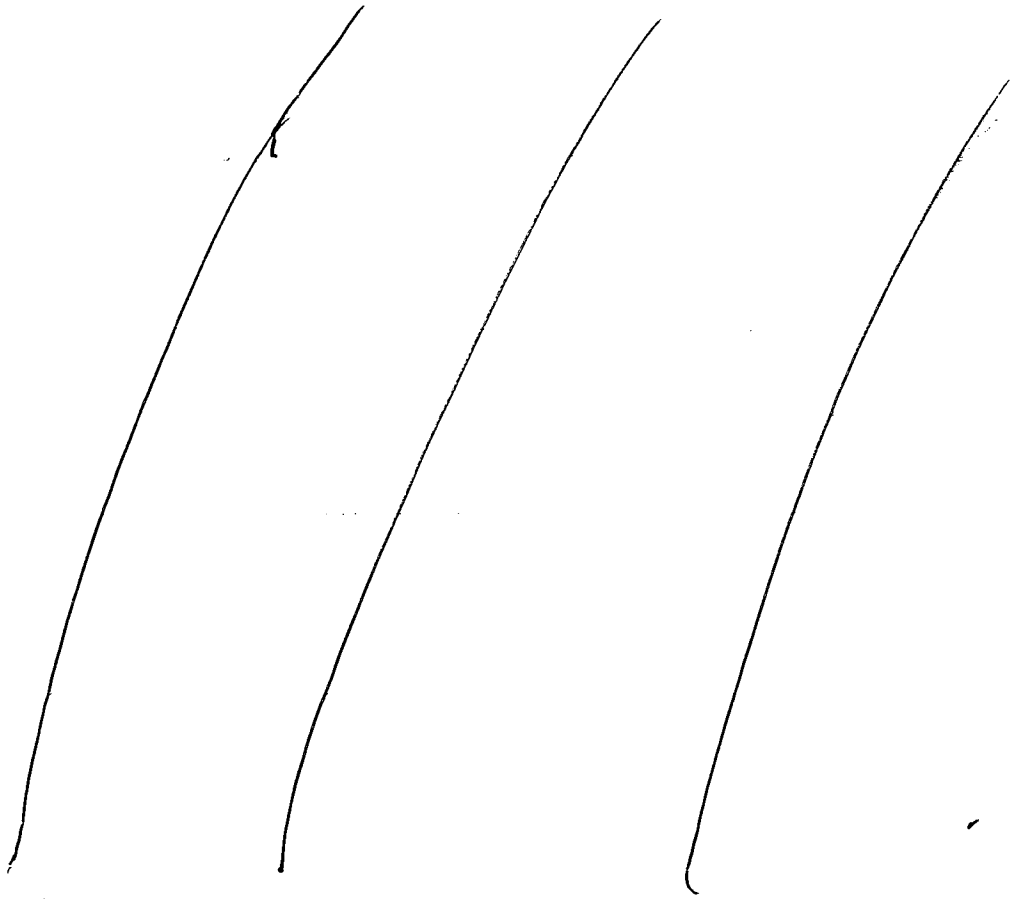
3.5.3 Division of Drug Marketing, Advertising and Communications (DDMAC)

DDMAC reviewed the proposed package insert (PI) for silodosin for possible promotional statements. DDMAC's comments are summarized below:



b(5)

b(5)



3.5.4 Division of Scientific Investigation (DSI)

DSI inspected four clinical sites where patients were enrolled into the two pivotal U.S. Phase 3 trials (studies SI04009 and SI04010). The sites were selected for inspection because they enrolled the largest numbers of subjects. In addition, the sponsor site, Watson Laboratories, was inspected because silodosin is a new molecular entity.

The DSI inspector concluded in his memorandum that "there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol. No underreporting of adverse events was noted. Overall, data generated for protocols SI04009 and SI04010 at these clinical sites appear acceptable for use in support of NDA 22-206."

3.5.5 Pediatric

b(5)

Rapaflo Waiver

- "NDA 22-206, Rapaflo (silodosin), was studied for BPH. The studies were submitted on December 13, 2007, and the PDUFA Goal Date is October 13, 2008.
- The Division is recommending a full waiver because studies are impossible or highly impractical because the disease does not exist in children. b(5)
-

3.5.6 Division of Pharmacovigilance II (DPV II)

The DPV II was consulted to review the post-marketing hepatic serious adverse event reports involving silodosin. The DPV II concluded that of the six cases they reviewed (a seventh was received after the consult request was made and was not reviewed), two were possibly related to use of silodosin. Therefore, DPV II suggests the following be specified in the product Approval Letter:

1) "The adverse event terms *jaundice* and ____ should be included in the postmarketing adverse events section of the silodosin label. b(4)
2) To ensure timely evaluation of serious ____ nepatic events (e.g. jaundice, hepatitis) the sponsor should submit all serious ____ nepatic events as expedited 15-day Alert Reports.
3) The sponsor should obtain comprehensive follow-up of all expedited reports of serious hepatic adverse events."

3.5.7 Microbiology

The microbiology reviewer recommended approval of the application from a microbiology perspective. No phase 4 commitments were requested.

The following is a summary of the key issues identified during the microbiology review of silodosin:

- The drug product is an oral capsule. The microbiology reviewer stated that there should be suitable controls on the ____ of the finished dosage form. b(4)
- The applicant did not submit release specifications for ____ of the drug product. In a July 10, 2008, amendment, the sponsor added a ____ test and acceptance criteria to the specification to the release of the drug product. The sponsor's proposal was considered acceptable by the microbiology reviewer. b(4)
- In the July 10, 2008, amendment, the sponsor also proposed a protocol by which they would confirm that production lots consistently meet ____ acceptance criteria, and that ____ b(4)
- During an August 11, 2008 teleconference with the Division, the sponsor ____

b(4)

b(4)

3.5.8 Interdisciplinary Review Team for QT Studies (IRT-QT)

The consultation from the IRT-QT is discussed in detail in section 7.1.9.3.

4. Data Sources, Review Strategy, and Data Integrity

4.1 Sources of Clinical Data

This review is based on the following information:

- Original submission for NDA 22-206 (December 11, 2007) containing the following (list is not inclusive):
  - Three controlled Phase 2/3 studies conducted in the U.S. (study KMD-3213-US021-99, SI04009, SI04010), open-label extension trial of U.S. Phase 3 studies (SI04011)
  - Thorough QT study (SI05014)
  - Foreign safety data – data from six Japanese Phase 2/3 studies and a single European Phase 3 trial
- 120-Day Safety Update for NDA 22-206 (April 11, 2008)

4.2 Tables of Clinical Studies

Table 4.1 shows the studies used to support the clinical efficacy and safety of silodosin for the US marketing application.

Table 4.1 Clinical studies supporting efficacy and efficacy of silodosin for NDA-22-206

Study Protocol	Duration of therapy (weeks)	Population	Dose	N on drug
KMD-3213-US021-99	8 weeks	Males 45-75, IPSS≥13, Qmax 4-15 ml/sec	4 mg and 8 mg	90 (8 mg) 90 (4 mg)
SI04009	12 weeks	Males≥50; IPSS≥13, Qmax 4-15 ml/sec; post-void residual <250 ml	8 mg	233
SI04010	12 weeks	Males≥50; IPSS≥13, Qmax 4-15 ml/sec; post-void residual <250 ml	8 mg	233
SI04011	40 weeks	Males≥50; IPSS≥13, Qmax 4-15 ml/sec; post-void residual <250 ml	8 mg	661
			Total on Drug	897 (on 8 mg)

A summary of clinical pharmacology studies which provided both pharmacokinetic and additional safety data on silodosin are shown in Table 4.2.

Table 4.2 Clinical Pharmacology Studies

Study No. (location)	Objective	Study Design	Doses studied	N/ type of subjects
95823 (Japan)	Single-dose PK study	Single-blind, crossover, single dose	0.5 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg	8 healthy adult males
95284 (Japan)	Repeated-dose PK study	Double-blind, repeated administration	2.5 mg once to three times daily x 7 days	9 healthy adult males
98363 (Japan)	Single-dose PK study	Single-blind, single administration	4 mg once, twice and three times	8 healthy adult males
98364 (Japan)	Repeated-dose PK study	Double-blind, repeated administration	4 mg bid, 6 mg bid, 8 mg bid x 7 days	8 healthy adult males
KMD3213-UK01-97 (UK)	Single-dose PK	Double-blind, single administration	1 mg, 2 mg, 4 mg, 2 mg x 2, 4 mg x 3, 4 mg x 4	12 healthy adult males
KMD3213-UK02-97	Repeated dose PK study	Double-blind, repeated dose	0.1 mg daily x 5 days; 1 mg daily x 5 days, 4 mg (2 mg capsules) daily x 5 days	12 healthy adult males
KMD3213-US011-09 (US)	Repeated dose, PK study	Double-blind repeated dose	4 mg once daily x 7 days 8 mg (two 4 mg capsules) once daily x 7 days 12 mg (three 4 mg capsules) x 7 days	12 healthy males
KMD-207 (Japan)	Repeated dose, PK study	Open-label, repeated administration study	6 mg (one 4 mg and one 2 mg capsule) twice daily x 7 days	12 healthy males
SI05008	Maximum tolerated dose study	Randomized, double-blind, placebo-controlled, dose escalation	16 mg, 24 mg, 32 mg, 40 mg and 48 mg once daily x 3 days	30 healthy adult males (6 per dose group)
KMD-308 (Japan)	Absolute bioavailability and food effect	Open-label, cross-over, single-dose	4 mg fasting and fed	12 healthy adult males
SI06004	Assess exposure of silodosin and four of its metabolites following administration of silodosin 8 mg once daily x 7 days	Single-center, open-label, multiple dose	8 mg (two 4 mg capsules) once daily x 7 days	19 healthy adult males
KMD3213-US012-99 (US)	PK study following single-administration of 14C-silodosin	Open-label, single administration	8 mg 14C-silodosin solution	6 healthy males

Pharmacokinetic data were also obtained in a subset of patients enrolled in U.S. Phase 2 study KMD3213-US021-99 and Phase 3 trial SI04009, and in two open-label Japanese safety studies, KMD-201 and KMD-305.

Additional clinical pharmacology studies were performed to assess the effects of intrinsic factors on the pharmacokinetics of silodosin. These studies are shown in Table 4.3

Table 4.3 Clinical Pharmacology Studies of effects of Intrinsic Factors on silodosin PK

Study No.	Objective	Design	Doses studied	N/type of subject
KMD-105 (Japan)	Single-dose PK study in the elderly	Open, single-dose	4 mg once	9 non-elderly males (aged 20-35 years) and 12 elderly males (≥65 years)
KMD-309 (Japan)	Single-dose PK study in subjects with renal impairment	Open, single-dose	4 mg once (fasting)	Adult males; N=7 with normal renal fxn; N=6 subjects with impaired renal fxn (creatinine clearance 11-50 ml/min)
SI05010 (US)	Single-dose PK study in subjects with hepatic dysfunction	Open-label, parallel, single-dose, cross-over	4 mg and 8 mg	Adult males aged 30-65 with moderate liver dysfunction (Child-Pugh score 7-9) and healthy age- and weight-matched controls
KMD-306-UK (UK)	Drug interaction study of single dose silodosin with ketoconazole 200 mg	Randomized, cross-over	Single dose of silodosin 4 mg alone and with ketoconazole 200 mg (given x 3 days)	16 healthy adult males
KMD-307-UK (UK)	Repeated-dose Drug interaction study of silodosin with digoxin	Double-blind, repeated dose	Digoxin 0.5 mg twice daily x 1 day, then 0.25 mg bid on days 2-16 with placebo or silodosin 4 mg bid administered days 9 to 16	26 healthy adult males
SI05014	Thorough QTc study	Double-blind, randomized, parallel group	Silodosin 8 mg or 24 mg x 5 days; placebo x 5 days; or moxifloxacin 400 mg once on Day 5	186 healthy adult men (split evenly among 4 dose groups)
SI06002	Drug interaction study with PDE5 inhibitor	Open-label, randomized, placebo-controlled, crossover	2 x 4 mg silodosin once daily x 21 days. 1 x 100 mg sildenafil or 1 x 20 mg tadalafil or placebo on days 7, 14 or 21	24 healthy men aged ≥45 years

4.3 Review Strategy

This review focused on the U.S. controlled Phase 2/3 trials (studies **KMD3213-US021-99), SI04009, SI04010**), the U.S. open-label safety extension (**SI04011**), the thorough QT study (**SI05014**), and the PDE-5 drug interaction study (**SI06002**). Special attention was paid to the appropriate dose of silodosin in the setting of renal impairment and concomitant administration of CYP3A4 inhibitors.

4.4 Data Quality and Integrity

An audit of the SAS datasets and case report forms from the U.S. Phase 2/3 uncontrolled and controlled studies confirms that verbatim terms were correctly coded and categorized to the preferred terms and "system, organ, class" using the standard MedDRA dictionary. There do not appear to be problems with data quality or integrity.

4.5 Compliance with Good Clinical Practices

All trials submitted to the NDA were conducted in accordance with good clinical practices.

4.6 Financial Disclosures

Financial disclosure was made for all required studies submitted to the NDA. There is no evidence to suggest that a financial relationship had any impact on the study results.

5. Clinical Pharmacology

During the silodosin development program, fourteen *in vitro* pharmacology studies were performed using human biomaterial. Twenty-one clinical pharmacology studies in 634 subjects (474 on silodosin; 113 on placebo; 47 on moxifloxacin) were performed to characterize the pharmacokinetics and pharmacodynamics of silodosin. In addition to the clinical pharmacology studies, four Phase 2/3 studies provided additional pharmacokinetic information from 644 patients (85 from study KMD-201, 9 from KMD 3213-US021-99, 258 from KMD-305, and 233 from SI04009).

5.1 Pharmacokinetics

The pharmacokinetics of silodosin has been evaluated in adult male subjects with and without BPH after single and/or repeated administrations with doses ranging from 0.1 mg to 48 mg per day.

5.1.1 Absorption and Exposure

The pharmacokinetics of silodosin 8 mg once daily were determined in a repeated-dose, open-label, 7-day pharmacokinetic study completed in 19 healthy, target aged (45 – 70 years) male subjects (study SI06004). Steady state pharmacokinetic parameters are shown in Table 5.1

Table 5.1 Steady State Pharmacokinetic Parameters for Silodosin

Cmax (ng/mL)	Tmax (hours)	T1/2 (hours)	AUCss, ng*hr/mL
61.6 +/- 27.54	2.6 +/- 0.90	13.3 +/- 8.07	373.4 +/- 164.94

The absolute bioavailability of silodosin following oral administration is approximately 32%.

5.1.2 Food Effect

Food decreases Cmax by approximately 30%, increases tmax by approximately 1 hour, and has little effect on AUC.

5.1.3 Distribution

The volume of distribution of silodosin following a single intravenous dose of 2 mg to healthy adult males was 49.5 L. The binding rate to plasma protein is 94.6 to 95.8%. The fractions of the major silodosin metabolites, KMD-3213G and KMD-3293, bound to human plasma protein were approximately 91% and 92%, respectively.

5.1.4 Metabolism

Silodosin is metabolized to a glucuronide conjugate, KMD-3213G via UGT2B7 (UDP-Glucuronosyltransferase-2B7). Its second major metabolite, KMD-3293, is formed via alcohol dehydrogenase and aldehyde dehydrogenase. A number of minor metabolites are formed via CYP3A4 pathway.

5.1.5 Excretion

Following administration of ^{14}C-silodosin to healthy subjects, 54.9% was recovered in feces and 33.5% was recovered in urine.

5.1.6 Effects of Intrinsic Factors on Pharmacokinetics

5.1.6.1 Age – A Phase 1 study was conducted to evaluate the effect of age on silodosin PK. The results indicate that elderly men (mean age 69 years old) had higher silodosin AUC (15.3% higher) and longer $t_{1/2}$ (21% longer) compared to young men (mean age 24 years old). There was no change in silodosin C_{max}. Exposure to KMD-3213G was about 44% higher in the elderly.

According to the DRUP clinical pharmacology reviewer, "since Phase 2 and Phase 3 safety and efficacy studies for silodosin were well represented by patients that were ≥65 years of age (42.8% or 384 out of 897 that were dosed at 8 mg silodosin once daily), no dosage adjustment is recommended for age."

5.1.6.2 Race – No clinical studies were performed to specifically investigate the effects of race. According to the DRUP clinical pharmacology review of NDA 22-206, "Cross-study comparison indicated that Japanese subjects on average had lower silodosin AUC and C_{max} and shorter $t_{1/2}$ than Caucasians and Blacks. However, the ranges of PK values overlapped between Japanese and Caucasian/Black populations."

5.1.6.3 Hepatic Impairment –A clinical pharmacology study (study SI05010) investigating the effects of hepatic dysfunction on silodosin metabolism was performed in 9 male subjects with moderate liver dysfunction (Child-Pugh score 7-9) and nine age- and weight-matched controls. Following a single dose of 4 mg or 8 mg silodosin, the the AUC and C_{max} of total (bound and unbound) silodosin were reduced by 26% in subjects with moderate hepatic dysfunction.

The effect of severe hepatic impairment on silodosin metabolism was not evaluated.

Reviewer's comment: The clinical pharmacology reviewer recommends, and this reviewer agrees, that no dose adjustment in patients with mild and moderate hepatic impairment is necessary.

As there are no data in subjects with severe hepatic impairment, silodosin should not be used in this population.

5.1.6.4 Renal Impairment -- A clinical pharmacology study (**KMD-309**) compared the pharmacokinetics of a single oral dose of 4 mg silodosin in Japanese subjects with moderate renal dysfunction (Ccr 27-49 mL/min) to controls with normal renal function. Renal dysfunction had a significant impact on the pharmacokinetics of silodosin – AUC of total (bound and unbound) silodosin and KMD3213G increased by 3.13 and 3.77-fold, respectively. C_{max} values for total silodosin and KMD 3213G were higher by 3.11- and 1.92-fold, respectively, in subjects with moderate renal impairment.

Reviewer's comment: Dosing recommendation for subjects with renal impairment is addressed in detail in section 8.2.

5.1.7 Effects of Extrinsic Factors on Pharmacokinetics

5.1.7.1 Drug-Drug Interactions

5.1.7.1.1 CYP3A4 inhibitors

As silodosin is a CYP3A4 substrate, two drug interaction studies (**KMD-306-UK** and **SI06008**) were performed with ketoconazole, a potent CYP3A4 inhibitor which also inhibits P-glycoprotein (P-gp).

In study KMD-306-UK, a two-period crossover trial, 16 healthy adult male subjects received ketoconazole 200 mg daily for four days (Day -1 to Day 3) alone, and in combination with silodosin 4 mg on Day 2. When administered concomitantly with ketoconazole, pharmacokinetic parameters of silodosin and its primary metabolites increased significantly (Table 5.2).

Table 5.2. Summary of Pharmacokinetic Parameters for Silodosin and its major metabolites following single oral doses of silodosin 4mg alone and in combination with ketoconazole 200 mg (Study KMD-306)

		Treatment		
Parameter	**Analyte**	**Silodosin + ketoconazole (N=16)**	**Silodosin N=16**	**Ratio (silodosin+ketoconazole/silodosin)**
AUC(0-∞) (ng.h/mL)	Silodosin	390	120	3.26
	KMD-3213G	1354	513	2.64
	KMD-3293	289	149	1.94
Cmax (ng/mL)	Silodosin	112	30.7	3.66
	KMD-3213G	68.4	25.2	2.71
	KMD-3293	32.2	15.8	2.05

Source: NDA 22-206, study report KMD-306, table 11.1-1

In study SI06008, an open-label crossover trial, 22 healthy adult male subjects received silodosin 8 mg alone and in combination with ketoconazole 400 mg. Co-administration of the two drugs led to a significant increase in silodosin C_{max} and AUC, similar to that observed in study KMD-306-UK (see Table 5.3).

Table 5.3. Summary of Pharmacokinetic Parameters for Silodosin and its major metabolites following single oral doses of silodosin 8 mg alone and in combination with ketoconazole 400 mg, study SI06008

		Treatment		
Parameter	**Analyte**	**Silodosin + ketoconazole (N=22)**	**Silodosin (N=22)**	**Ratio (silodosin+ketoconazole/silodosin)**
AUC(0-∞) (ng.h/mL)	Silodosin	1159.1	378.1	3.1
	KMD-3213G	3528.6	1186.7	3.0
	KMD-3293	854	344.1	2.6
Cmax (ng/mL)	Silodosin	234.4	63.7	3.7
	KMD-3213G	184.4	58.0	3.2
	KMD-3293	100.2	35.2	2.84

Source: NDA 22-206, study report SI06008, table 11.3.1-2 – 11.3.3-2

Reviewer's comment: According to the DRUP clinical pharmacology reviewer, although ketoconazole co-administration increased both the AUC and Cmax of silodosin and its metabolism, silodosin's elimination $t_{1/2}$ was not changed. He writes in his review, "Because ketoconazole may potentially inhibit the transporter P-glycoprotein (P-gp) and silodosin is a P-gp substrate, it is not clear if the observed effects are due to inhibition of CYP3A4 or P-gp or both. Until this issue is resolved, labeling should encompass both pathways."

Because of the risk of hypotension, this reviewer believes that silodosin should be contraindicated with concomitant potent CYP3A4 inhibitors. The effect of moderate CYP3A4 inhibitors on silodosin metabolism has not been studied. Further discussion is found in section 8.2.1.

The clinical pharmacology reviewer recommends, and this reviewer agrees, that use of silodosin is not advised in patients taking strong P-gp inhibitors (e.g. cyclosporine).

5.1.7.1.2

The interaction between silodosin and digoxin, a P-glycoprotein substrate with a narrow therapeutic index, was investigated in a Phase 1, double-blind, placebo-controlled study **(KMD-307-UK)**. Twenty-four healthy male subjects received a loading dose of digoxin (0.5 mg bid x 1 day), followed by 0.25 mg daily for 15 days (Days 2-16). Silodosin 4 mg or placebo bid was co-administered with digoxin on Days 9 to 16.

Co-administration of silodosin did not significantly affect the PK of digoxin, as shown in Table 5.4.

Table 5.4. Comparisons between Digoxin Pharmacokinetic Parameters with and without Silodosin (study KMD-307-UK)

Treatment	Parameter	Geometric least squares mean		Ratio of means (Day 16:Day 8)
		Day 8	Day 16	
Digoxin + silodosin	AUC(0-∞)	14.7	14.4	0.984
	Cmax	1.26	1.25	0.992
Digoxin + placebo	AUC(0-∞)	15.0	14.5	0.968
	Cmax	1.22	1.15	0.942

Source: NDA 22-206 ser 000, KMD-307-UK study report, Table 14.2-1

Reviewer's comment: No dose adjustment is recommended in patients taking digoxin (see also section 8.2.2).

5.2 Pharmacodynamics

Refer to the Section 6, Efficacy Review, for discussion of the effect of silodosin on lower urinary tract symptoms, and Section 7, Safety Review, for information on silodosin's effect on blood pressure.

5.2.1 Pharmacodynamic Drug-Drug Interactions – PDE-5 inhibitors

A complete discussion of the interaction of silodosin with PDE-5 inhibitors is found in section 7.4.2.5.3.

5.4 Exposure-Response Relationship

The sponsor believes that results of the U.S. Phase 2 clinical trial, KMD3213-US021-99, demonstrate that 8 mg silodosin is more effective in treating BPH symptoms than 4 mg silodosin. Although the 4 mg dose met statistical significance for efficacy on the total IPSS (a co-primary endpoint), the effect was not as robust as that seen with the 8 mg dose. In addition, the change from baseline in Qmax (co-primary endpoint) was not statistically significant for the 4 mg dose (results shown in Table 5.5).

Table 5.5 Placebo-Subtracted Mean Change from baseline to week 8/LOCF in co-primary endpoints, total AUA-SS and Q_{max}, US Phase 2 study, KMD3213-US021-99

Primary Efficacy Variable	8 mg silodosin N=90	4 mg silodosin N=88
IPSS total score	-2.8	-1.6
p-value (vs. placebo)	0.0018	0.0355
Q_{max}	+1.9	+1.4
p-value (vs. placebo)	0.0174	0.0966

Source: NDA 22-206 ser 000, KMD3213-US-021-99 study report, Tables 5.1 and 5.2

Reviewer's comment: The sponsor's rationale is acceptable. As discussed in Sections 7.4.2.1 and 8.1, the 8 mg dose does not pose an increased risk to patients and appears to provide a modest therapeutic benefit over the 4 mg dose.

6. Integrated Review of Efficacy

6.1 Indication

Silodosin is proposed for the "treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)."

6.1.1 Methods

In support of clinical efficacy, the sponsor submitted the results of three placebo-controlled Phase 2/3 studies conducted in the US in 1,187 patients with BPH.

Table 6.1 US Controlled Phase 2/3 studies for BPH indication

Study	Phase	Silodosin Dose	N enrolled	N on drug
KMD3213-US021-99	2	4 mg or 8 mg once daily	264	88 on 4 mg 89 on 8 mg
SI04009	3	8 mg once daily	461	233 on 8 mg
SI04010	3	8 mg once daily	462	233 on 8 mg
Total			1187	643 on drug; 555 on 8 mg

6.1.2 General discussion of endpoints

The primary endpoint in all three controlled studies was the change from baseline to last observation carried forward (LOCF) in the International Prostate Symptom Score (IPSS) (also known as the AUA-SS) total score. Change from baseline in maximum urinary flow rate (Qmax) was a co-primary endpoint in the Phase 2 study, KMD-3213-US021-99.

Baseline was defined as the last non-missing data prior to receiving study treatment. LOCF was defined as the last non-missing data obtained during the treatment period.

Qmax was a pre-specified secondary endpoint in the two Phase 3 trials, SI04009 and SI04010. Additional secondary endpoints in all three studies were the irritative and obstructive subscales of the IPSS and a quality of life question.

Reviewer's comments:
1) Change in total IPSS and Qmax are standard efficacy endpoints used in BPH clinical trials and are accepted by DRUP.

2) In a May 2, 2005, letter to the sponsor regarding protocols for Phase 3 studies SI04009 and SI04010, DRUP wrote, "The primary endpoint is the IPSS. We consider the quality of life question and the IPSS sub-scores of irritative and obstructive voiding symptoms [to be] secondary exploratory endpoints."

6.1.3 Study Design

The trials were randomized, double-blind, placebo-controlled, parallel-group studies in patients with BPH which was defined as an IPSS $\geq$13 and Q_{max} of 4-15 mL/sec with a minimum voided volume of 125 mL.

Study KMD3213-US021-99

This Phase 2 study was comprised of three periods: a 4-week placebo run-in period, a 2-week dose adjustment period and a 6-week stable dosing period. Following the placebo run-in period, 264 eligible patients, aged 45-75 years, were randomized as follows:

- 8 mg silodosin (n=90)
- 4 mg silodosin (n=88)
- Placebo (n=86).

Studies SI04009 and SI04010:

These studies consisted of two periods -- a 4-week single-blind placebo run-in and a 12-week dosing period. Four-hundred and sixty-one eligible patients, aged $\geq$50 years, were randomized to either 8 mg silodosin (N=233 in each study) or placebo (N=228 in each study) administered once daily.

The design of these Phase 3 trials was identical except that plasma concentration data were not collected in study SI04010.

6.1.4 Efficacy Findings

6.1.4.1 General Efficacy

Efficacy data from the U.S. controlled Phase 2 study and the U.S. Phase 3 pivotal studies were integrated for combined efficacy analysis. As the Phase 2 study included both a 4 mg and 8 mg dose group, only data from the 8 mg and placebo dose groups were integrated into the efficacy analysis

For all US controlled studies, the effect of silodosin 8 mg daily on symptoms of BPH as measured by change from baseline in the IPSS total score exceeded that of placebo in a statistically significant manner ($p<0.0001$) (Table 6.2).

Table 6. 2 Summary of Change from Baseline to LOCF in Total IPSS Score – All US Controlled Studies (Phase 2 Study and 2 Phase 3 studies) (mITT population)[1]

Study	Visit	Statistic	Placebo	Silodosin	p-value
			N=540	N=556	
Overall	Endpoint (LOCF)	Mean (SD)	-3.6 (5.79)	-6.4 (6.5)	<0.001

Source: NDA 22-206 ser 000, ISE, Table 3.5-1

1 – For the Phase 3 studies, the modified intent-to-treat (mITT) population consisted of all randomized patients who provided data for the primary efficacy variable at baseline. If a patient was mis-randomized, then the actual treatment given was used in all summary statistics and analyses.
For the Phase 2 study, the mITT population included all randomized patients with a baseline evaluation and at least one post-baseline AUA symptom score or Qmax measurement.

For all US controlled studies, silodosin's effect on symptoms of BPH as measured by a change from baseline in Qmax exceeded that of placebo in a statistically significant manner ($p<0.0002$) (Table 6.3).

Table 6.3. Summary of Change from Baseline to LOCF in Qmax – All US Controlled Studies (Phase 2 Study and 2 Phase 3 studies) (mITT population)

Study	Visit	Statistic	Placebo	Silodosin	p-value
			N=540	N=556	
Overall	Endpoint (LOCF)	Mean (SD)	+1.6 (4.39)	+2.7 (4.68)	0.0002

Source: NDA 22-206 ser 000, ISE, Table 3.61

In the U.S. Phase 3 controlled studies, silodosin 8 mg once daily resulted in a statistically significant decrease in total IPSS and an increase in Qmax over placebo ($p<0.0001$ and $p=0.0007$, respectively) (Tables 6.4 and 6.5).

Table 6.4 Summary of Change from Baseline to week 12/LOCF in Total IPSS Score – US Phase 3 Controlled Studies (mITT population)[1]

Study	Visit	Statistic	Placebo	Silodosin	p-value
			N=457	N=466	
Overall	Endpoint (LOCF)	Mean (SD)	-3.5 (5.84)	-6.4 (6.63)	<0.001

Source: NDA 22-206 ser 000, ISE, Table 2.1-4

Table 6.5 Summary of Change from Baseline to week 12/LOCF in Qmax (ml/sec) – US Phase 3 Controlled Studies (mITT population)[1]

Study	Visit	Statistic	Placebo	Silodosin	p-value
			N=457	N=466	
Overall	Endpoint (LOCF)	Mean (SD)	1.5 (4.36)	2.6 (4.43)	0.0007

Source: NDA 22-206 ser 000, ISE, Table 2.5-4

Results from the two individual Phase 3 trials are shown in Tables 6.6 and 6.7.

Table 6.6. Summary of Change from Baseline to week 12 (LOCF) in IPSS – Phase 3 studies SI04009 and SI04010

Study	Visit	Statistic	Placebo	Silodosin	p-value
SI04009			N=228	N=233	
	Week 12 (LOCF)	Mean (SD)	-3.6 (5.85	-6.5 (6.73)	<0.0001
SI04010			N=229	N=233	
	Week 12 (LOCF)	Mean (SD)	-3.4 (5.83)	-6.3 (6.54)	<0.0001

Source: NDA 22-206 ser 000, SI04009 study report, Table 11.4.1-2 and SI04010 study report, Table 11.4.1-2

Table 6.7. Summary of Change from Baseline to week 12 (LOCF) in Qmax – Phase 3 studies SI04009 and SI04010

Study	Visit	Statistic	Placebo	Silodosin	p-value
SI04009			N=228	N=233	
	Week 12 (LOCF)	Mean (SD)	+1.2 (3.81)	+2.2 (4.31)	0.0060
SI04010			N=229	N=233	
	Week 12 (LOCF)	Mean (SD)	+1.9 (4.82)	+2.9 (4.53)	0.0431

Source: NDA 22-206 ser 000, SI04009 study report, Table 11.4.1-7 and SI04010 study report, Table 11.4.1-7

6.1.4.2 Efficacy in Subgroups

A retrospective sub-group analysis of the effect of age and race on silodosin efficacy was performed by the sponsor. Results of these analyses are shown in Tables 6.8 and 6.9. P-values are not presented since these analyses were not pre-specified.

Table 6.8 Summary of Mean Change from baseline to endpoint in IPSS Total Score and Qmax (ml/sec) by Age Group – All US Phase 2/3 Controlled Studies

	<65		≥65		<75		≥75	
	Placebo N=309	Silodosin N=323	Placebo n=231	Silodosin N=233	Placebo N=484	Silodosin N=495	Placebo N=56	Silodosin N=61
Total IPSS	-3.8	-6.7	-3.4	-6.0	-3.6	-6.5	-3.5	-6.1
Qmax	+1.7	+2.8	+1.5	+2.6	+1.6	+2.8	+1.3	+2.2

Table 6.9 Summary of Mean (SD) Change from Baseline to LOCF in IPSS Total Score and Qmax by Race – All US Controlled Studies (mITT population)

	Caucasian		Non-Caucasian	
	Placebo (n=472)	Silodosin (N=507)	Placebo (n=68)	Silodosin (n=49)
Total IPSS	-3.4 (5.60)	-6.3 (6.41)	-5.0 (6.92)	-7.8 (7.28)
Qmax	1.6 (4.31)	2.6 (4.64)	1.7 (4.98)	3.1 (5.08)

Reviewer's comment: Although the Division [redacted] *, these data suggest that efficacy of silodosin is not affected by age or race.*

b(4)

6.1.4.3 Long-term Efficacy Data

Study SI04011 was a multi-center, 40-week, open-label extension for BPH patients who had previously completed Phase 3 study SI04009 or SI04010. Six-hundred and sixty-one men enrolled. Efficacy was assessed by change from baseline in total IPSS score. Baseline was defined as the last visit of the double-blind study.

During the 9-month treatment period, there was a mean decrease of 3.1 points in the IPSS total score. Patients who had previously received placebo during the double-blind treatment period had a larger response than those who had received silodosin (Table 6.10).

Table 6.20. Mean (SD) Change from Baseline (Week 0)* to Week 40 (LOCF) in IPSS Total Score

Assessment	Treatment Received during Double Blind Study		Overall N=429
	Placebo N=223	Silodosin N=206	
IPSS Total Score	-4.4 (6.71)	-1.6 (5.92)	-3.1 (6.49)
*baseline/week 0 = last visit of double-blind study			

6.1.5 Efficacy Conclusions

Data from three US controlled Phase 2/3 studies in 1,187 patients with BPH support the efficacy of silodosin 8 mg once daily in the treatment of the signs and symptoms of BPH.

Data from the open-label extension study suggest that efficacy is maintained for up to 9 months of treatment.

7. Integrated Review of Safety

7.1 Methods and Findings

This review focuses primarily on the U.S. safety database which consists of four Phase 2/3 trials –

- Placebo-controlled Phase 2 study KMD3213-US021-99 (N=264)
- Placebo-controlled Phase 3 studies SI04009 (N=461) and SI04010 (N=462)
- Open-label safety extension of Phase 3 studies, SI04011 (N=661)

Review of Japanese (Phase 1 through Phase 3) and European Phase 3 clinical trials data are limited to deaths and any significant safety signal identified during the primary database analysis.

To evaluate the accuracy of adverse event coding, investigator verbatim adverse event terms for a select sample of patients was compared to the corresponding preferred terms assigned by the sponsor.

7.1.1 Deaths

In the four silodosin Phase 2/3 studies conducted in the U.S., there were three deaths – two in patients receiving silodosin and one in a placebo-treated subject. The silodosin deaths both occurred in the open-label safety extension, SI04011. Narratives are found below.

Patient 259027 This patient was a 58 year old, markedly obese (164kg) Caucasian male who was randomized to placebo in the double-blind Phase of study SI04010 from November 8, 2005, to March 13, 2006. He entered study SI04011 on March 14, 2006. His past medical history included abdominal hernia, obstructive sleep apnea and left carotid bruit. Baseline 12-lead ECG showed sinus arrhythmia with left bundle branch block. The patient was on no concomitant prescription medications.

b(6)

On [redacted], the patient experienced a fatal myocardial infarction. According to the death certificate, the cause of death was listed as acute MI due to severe coronary atherosclerosis. The investigator assessed the event as not related to study drug.

Patient 133032 This patient was a 79-year-old Caucasian male who was randomized to silodosin in the double-blind Phase of study SI04009 from October 25, 2005 to January 22, 2006. He entered study SI04011 on January 23, 2006. The patient had a past medical history of chronic bronchitis, bilateral knee arthritis and GERD. Concomitant medications were Naprosyn 500 mg bid and Nexium 40 mg daily.

On [redacted], the patient was hospitalized for an elective left total knee replacement. Silodosin was discontinued on September 24, 2006, prior to surgery. The patient was discharged to a nursing home for physical rehabilitation on [redacted]. On [redacted] the patient experienced acute shortness of breath with subsequent cardiopulmonary arrest and death. The diagnosis of probably pulmonary embolus was made at the time of death. The investigator assessed the adverse event as not related to study drug.

b(6)

Reviewer's comment: This reviewer agrees with the investigators' assessments that the two deaths do not appear to be related to silodosin therapy.

No deaths were reported in U.S. Phase 1 studies, in Japanese clinical trials, or in the European Phase 3 trial.

7.1.2 Other Serious Adverse Events

7.1.2.1 Controlled Trial Database

In US controlled Phase 3 studies, seventeen serious adverse events (SAEs) were reported in 13 patients (6 on silodosin, 7 on placebo) during the double-blind treatment period. These SAEs are displayed in Table 1. No SAEs were reported in the U.S. controlled Phase 2 study.

Table 7.1 Serious Adverse Events Occurring in US controlled Phase 3 trials (SI04010 and SI04009)

Patient ID	SAE (s)	Pt medical history	Time on drug at onset of AE	Action Taken	Relation to therapy (investigator assessment)
Silodosin Cases					
SI04009/ 136019	Acute myocardial infarction (MI)	65M h/o CAD, COPD	23 days	Drug d/c'd	unrelated
	Congestive heart failure				
	Enterococcal bacteremia				
	Respiratory failure				
SI04009/ 101027	Cervical radiculopathy	68M h/o htn, b/l OA (hips)	20 days	Treatment interrupted	unrelated
SI04009/ 112028	Acute MI	70M h/o hypothyroidism	74 days	Drug d/c'd	Unrelated
SI04010/ 272046	Syncope	85M h/o DM, PVD, HTN, CAD	2 days	Drug d/c'd	Related
SI04010/ 259003	Complete heart block	69M h/o DM, HTN, hi chol, type 1 second degree AV block	39 days	None (drug not d/c'd)	unrelated
SI04010/ 295024	Carotid artery stenosis aggravated	63M h/o carotid stenosis, DM, HTN, CAD	80	None	Unrelated
Placebo cases					
SI04010/ 273015	Rotator cuff tear	60M	3 days	none	unrelated
SI04010/ 278045	Bacterial enterocolitis	60M h/o hi chol	67 days	interrupted	Unrelated
	Acute renal failure				Unrelated
SI04010/ 285011	Removal of vocal cord lesion	60M h/o vocal cord lesion, anxiety	18 days	Interrupted	Unrelated
SI04010/ 287010	Suicidal ideation	62M h/o depression	7 days	Discontinued	Unrelated
SI04009/ 103008	Small bowel obstruction	74M h/o CAD, PVD	62 days	Discontinued	Unrelated
	Myocardial infarction				unrelated
SI04009/ 105013	Gastrointestinal bleed	55M	Occurred during placebo run-in	Interrupted	unrelated
SI04009/ 106028	diverticulitis	58M h/o diverticulitis		Discontinued	Unrelated

Reviewer's comment: Narratives for all SAEs were reviewed. Only the case of syncope (SI04010-272046) appears to be possibly related to study drug. Narrative of this report can be found in Appendix C, summary of study SI04010.

No pattern was evident among SAEs in the silodosin group.

7.1.2.1 U.S. Phase 3 Open-label Database

In study SI04011, the 40-week open-label extension study, 29 patients experienced 35 serious adverse events: osteoarthritis (4 events); lung neoplasm malignant (3 events); diverticulitis (2 events); hip arthroplasty (2 events); atrial fibrillation (2 events); prostate cancer (2 events); pulmonary embolism (2 events); myocardial infarction (2 events); and one event each of abdominal aortic aneurysm repair; back injury; status-post fall injury/severe concussion; knee arthroplasty; nerve root lesion; deep vein thrombosis; spinal laminectomy; arrhythmia, arthralgia; squamous cell carcinoma (throat); acute gastritis; pain in extremity; femoral artery occlusion; transient ischemic attack; lobar pneumonia; and aggravated carotid artery stenosis. None of the SAEs was considered by the investigator to be related to silodosin.

Reviewer's comment: Narrative summaries of the SAE's were reviewed. A relationship to silodosin can be reasonably excluded in nearly all cases except that of patient 126031 (s/p fall injury/severe concussion), which is described below.

> **Patient 126031** was a 60-year-old male, who was randomized to silodosin in the double blind Phase of clinical study SI04009. He entered the open-label Phase of study SI04011 study on March 23, 2006. The patient had a past medical history of myocardial infarction and coronary artery stent placement in [redacted] and hypercholesterolemia since 1997.
>
> On [redacted] while he was at work, the patient fell off a ladder to the floor, dropping an industrial stapler on the top of his head. The patient was brought to the emergency room, where he complained of dizziness and headache. He could not recall the date or the medication that he was taking at that time. b(6)
>
> The patient was admitted to the hospital for five days with the diagnosis of post-fall injury/severe concussion with laceration to the scalp, headache, dizziness, vomiting, lethargy, slight memory loss and fever. Infectious origin of fever was excluded by negative urinalysis and blood, body fluid, CSF and bilateral nasal swab cultures. The patient was discharged home on [redacted] b(6)
>
> Silodosin therapy was interrupted for five days but was not discontinued. The investigator assessed the event of post-fall injury/ severe concussion as serious and not related to the study drug.
>
> *Reviewer's comment: The cause of the patient's fall (e.g. pre-syncope vs. lost footing) is not clarified. Without that information, the possibility of silodosin contributing to the fall can not be excluded.*

7.1.3 Dropouts and Other Significant Adverse Events (AEs)

In the integrated U.S. safety database (controlled and uncontrolled Phase 2/3 trials) 127 patients discontinued prematurely due to an adverse event. Retrograde ejaculation, which occurred in 5.5% of silodosin patients, was the most common AE leading to discontinuation.

In U.S. controlled Phase 3 trials, dropouts due to AEs were more common among silodosin-treated patients than those on placebo (12.9% versus 4.3%, respectively). The most common AEs leading to discontinuation among silodosin patients in these trials are shown in Table 7.2.

Table 7.2. AEs leading to early discontinuation, US Controlled Phase 3 trials

Adverse Event (Preferred term)	Silodosin N=466	Placebo N=457
Retrograde ejaculation	13 (2.7%)	0
Dizziness	2 (0.4)	1 (0.2)
Orthostatic hypotension	2 (0.4)	0
Syncope	1 (0.2)	0

Source: NDA 22-206 ser 000, ISS, Table 2.2.1-12

In the open-label safety extension (SI04011), eighty-six patients (13.0%) discontinued prematurely due to an adverse event emerging during the open-label period. The most common AEs resulting in discontinuation were retrograde ejaculation (4.8%), diarrhea (0.8%), libido decreased (0.6%), dizziness (0.5%), and lung neoplasm malignant (0.5%). The events of retrograde ejaculation, diarrhea, libido decreased and dizziness were considered related to study drug, but lung neoplasm was considered unrelated. Notably, a single patient in this study discontinued due to the adverse event of intra-operative floppy iris syndrome.

7.1.4 Common Adverse Events

7.1.4.1 Eliciting adverse events data in the development program

In U.S. Phase 2/3 trials, subjects were queried for adverse events at baseline and at each follow-up clinic visit. Data obtained included a description of the event, onset and resolution dates, treatment required, action taken, outcome, and the investigator's assessment of seriousness of the event and relationship to study drug.

7.1.4.2 Appropriateness of adverse event categorization and preferred terms

Adverse events initially recorded by study personnel ("verbatim term") were subsequently mapped to a "preferred" term from the Medical Dictionary for Drug Regulatory Affairs (MedDRA). An audit of case report forms from the four Phase 2/3 trials finds that verbatim terms were appropriately categorized.

7.1.4.3 Incidence of common adverse events

From all four US Phase 2/3 studies, treatment-emergent adverse events occurring in ≥1% of patients are shown in Table 7.3.

Table 7.3 Summary of Treatment-Emergent Adverse Events Occurring in >1% of Patients (All U.S. Controlled and Uncontrolled Trials)

Adverse Event – Preferred Term	Percentage (N=897)
retrograde ejaculation	31.9
diarrhea	4.8
dizziness	3.8
nasopharyngitis	3.8
orthostatic hypotension	3.2
headache	2.7
nasal congestion	2.7
URI	2.5
PSA increased	2.3
arthralgia	2.2
hypertension	2.0
Sinusitis	1.8
Back pain	1.6
Cough	1.4
Erectile dysfunction	1.4
Libido decreased	1.4
Urinary tract infection	1.4
Influenza	1.3
Abdominal pain	1.2
Bronchitis	1.1
Sinusitis	1.1
Blood urine present	1.0
GGT increased	1.0
Nausea	1.0
Pharyngolaryngeal pain	1.0

Source: NDA 22-206 ser 000, Table 2.5.3

Treatment-emergent adverse events that occurred in ≥2% of patients receiving silodosin in Phase 3 controlled trials, and at an incidence numerically higher than that of placebo are shown in Table 7.4.

Table 7.4 Treatment-emergent adverse events occurring in >2% of silodosin patients, U.S. Controlled Phase 3 trials

Adverse Event – preferred term	Silodosin N=466 n (%)	Placebo N= 457 n (%)
Retrograde ejaculation	131 (28.1)	4 (0.9)
Dizziness	15 (3.2)	5 (1.1)
Diarrhea	12 (2.6)	6 (1.3)
Orthostatic hypotension	12 (2.6)	7 (1.5)
Headache	11 (2.4)	4 (0.9)
Nasopharyngitis	11 (2.4)	10 (2.2)
Nasal congestion	10 (2.1)	1 (0.2)

Source: NDA 22-206 ser 000, Table 2.5.4

Reviewer's comment: Common treatment-emergent adverse events with silodosin are consistent with those reported for other alpha-1-adrenergic receptor antagonists. For comparison, 6.3% of Uroxatral® treated subjects experienced orthostatic symptoms (AE terms dizziness, hypotension or syncope) in 3-month placebo-controlled clinical trials of Uroxatral®.[3]

The incidence of retrograde ejaculation with silodosin is substantially higher than that reported in clinical trials of currently marketed alpha-1-antagonists (e.g. 18% for tamsulosin 0.8 mg).[4] *This effect, though undesirable, is reversible and is not a risk to a patient's health.*

7.1.5 Laboratory Findings

7.1.5.1 Overview of laboratory testing in the development program

Laboratory data from the Phase 2 study KMD-3213-US021-99 were not integrated into the safety summary because they were in a different format and therefore incompatible with data from the Phase 3 trials.

In the two controlled Phase 3 trials, clinical laboratory tests (serum chemistry, hematology and urinalysis) were performed at screening, Visits 1, 7 and 8 (weeks -4, 4 and 12 relative to drug initiation, respectively). Tests for HgbA1C, PSA, TSH, T3, free and total T4, and prolactin were performed at screening and the end-of-treatment visit (week 12).

In the open-label safety extension study (**SI04011**), laboratory parameters (serum chemistries, hematology, and urinalysis) were measured at week 8, 16 and 40 (or discharge). In addition, PSA and thyroid function tests were obtained at week 40 (or discharge).

Reviewer's comment: The Division recommended that prolactin levels be monitored because of an increased incidence of mammary gland neoplasms observed in preclinical studies of silodosin in female rats.

Thyroid monitoring was performed because of thyroid follicular adenomas observed in male rats treated with silodosin.

It is not clear why HgbA1C was monitored during the Phase 3 trials.

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[3] Uroxatral® approved label, dated, March 29, 2007.
[4] Flomax® approved label, dated, February 15, 2007.

7.1.5.2 Standard analyses and exploration of laboratory data.

Central tendency and outlier analyses were performed to screen for potential laboratory safety signals.

7.1.5.2.1 Hematology

In both controlled Phase 3 studies and the open-label extension study, there was no significant difference in mean change from baseline to endpoint in any hematology parameter between placebo and silodosin treatment groups.

Compared to placebo, there was also no significant difference in the percentage of silodosin subjects in controlled Phase 3 trials experiencing a shift from normal to abnormal in any hematology parameter.

In the Phase 3 open-label extension, there was no significant change from baseline to endpoint in any hematology parameter.

7.1.5.2.2 Chemistry

Compared to placebo, silodosin subjects in controlled Phase 3 trials experienced a slightly greater change from baseline in mean and median serum ALT and serum glucose at all time points measured (Table 7.5).

Table 7.5 Change from baseline in serum ALT, Glucose, U.S. Controlled Trials (Safety Population)

Analyte	Visit	Statistic	Placebo (N=457)	Silodosin (N=466)
ALT	>0 – 6 weeks	Mean (SD)	0.4 (6.66)	1.3 (7.23)
		Median	0.0	1.0
	>6 weeks	Mean (SD)	1.4 (8.09)	1.9 (8.25)
		Median	1.0	2.0
	Last observation	Mean (SD)	1.3 (7.94)	2.0 (8.08)
		Median	1.0	2.0
Glucose, random serum	>0 – 6 weeks	Mean	1.3 (22.03)	5.5 (27.39)
		Median	0.0	2.0
	>6 weeks	Mean (SD)	1.3 (27.99)	3.6 (26.32)
		Median	-1.0	1.0
	Last observation	Mean (SD)	1.5 (27.76)	3.7 (26.11)
		Median	-1.0	1.0

Source: NDA 22-206 ser 000, integrated summary of safety, Table 2.4.1-5

In study SI04011, there was no meaningful change in mean serum chemistries up to 40 weeks.

In controlled Phase 3 trials, more silodosin patients than those on placebo experienced a shift from "normal" at baseline to "high" on treatment in serum AST, GGT and creatinine (Table 7.6).

Table 7.6 Summary of Patients experiencing a shift in serum chemistry parameters from "normal" to "high" during treatment – U.S. Controlled Phase 3 trials (Safety Population)

Analyte	Study Visit	placebo	silodosin
AST	>0-6 weeks	8/435 (1.8%)	12/432 (2.8%)
	>6 weeks	5/417 (1.2%)	12/414 (2.9%)
	Last observation	5/442 (1.1%)	13/452 (2.9%)
Creatinine	>0-6 weeks	5/435 (1.1)	3/423 (0.7%)
	>6 weeks	4/417 (1.0)	8/416 (1.9%)
	Last observation	4/442 (0.9%)	8/454 (1.8%)
GGT	>0-6 weeks	11/435 (2.5%)	12/432 (2.8%)
	>6 weeks	11/417 (2.6%)	17/416 (4.1%)
	Last observation	12/442 (2.7%)	18/454 (4.0%)

Comparing Tables 7.5 and 7.6, there are no laboratory values that consistently show a positive signal based on both central tendency and outlier analysis. However, a transaminase (serum ALT or AST) is represented in both mean and outlier analyses. Further investigation is conducted on serum liver function tests (section 7.1.8) and other chemistry outliers (7.1.7.2.2.1).

7.1.5.2.2.1 Further Laboratory Investigation: Chemistry Outliers

In the 74-day letter to the sponsor, the Division commented that the clinical significance of a greater number of silodosin subjects experiencing a shift from normal to high in serum AST, creatinine and GGT was unclear but would be a review issue. The sponsor responded to this comment in a submission dated June 3, 2008, that addressed silodosin's effects on these laboratory parameters. Changes in serum GGT and AST are addressed in section 7.1.7.2.2.2, liver function tests. A discussion of serum creatinine is found below.

Creatinine

In U.S. controlled Phase 3 trials, the mean change for serum creatinine from baseline to each time point measured was 0.0 for both silodosin and placebo groups. In addition, in the open-label study SI04011, there was no change in mean serum creatinine at any time point during the course of the 40-week study.

The controlled Phase 3 database was searched by this reviewer for subjects whose creatinine shifted from normal at baseline to high on treatment. Fourteen silodosin subjects and eight placebo subjects met this criterion. However, among the fourteen silodosin subjects, five continued in the open-label extension study and their creatinine normalized while still on silodosin. Therefore, a similar number of silodosin patients had shifts from normal to high compared to placebo (9 versus 8).

The magnitude of the shift in serum creatinine was larger for placebo patients compared to silodosin patients (mean of 0.475 mg/dl versus 0.288 mg/dL respectively) when excluding silodosin patient *278013* who had a shift of 3.6 mg/dL. Narrative of patient *278013* is found below.

Patient *278013* was a 71-year-old white male with a history of BPH, allergic rhinitis, hyperlipidemia, hepatitis and arthritis. He completed study SI04010 but did not enroll in the open-label study SI04011. He was randomized to silodosin on August 17, 2005, and received silodosin for 73 days. Time course of his serum creatinine and BUN is presented in the figure below.

Figure 7.1 Laboratory Values, Patient *278013*

Lab/Date	06 Jul 05	20 Jul 05	21 Sep 05	28 Oct 05
Visit	Scr	V1	V7	V8
Creatinine	1.6	1.4	1.7	5.0
BUN	22	17	18	37

Scr = Screening Visit
Shaded cells are out-of-range
Bold vertical bar represents end of placebo lead-in and start of silodosin therapy

Source: NDA 22-206, ser 0005, submitted 6/3/08

Because of the abnormal laboratory values, the patient was referred for follow-up and was subsequently diagnosed as having renal failure secondary to multiple myeloma.

The sponsor concluded in their follow-up submission dated June 3, 2008, that silodosin has no meaningful effect on serum creatinine values.

Reviewer's comment: This reviewer agrees that, based on the available data, silodosin has no meaningful effect on serum creatinine.

7.1.5.2.3 Other Laboratory

In controlled Phase 3 trials, no significant difference was observed in mean change from baseline to week 12/end-of-treatment in serum thyroid parameters (TSH, total T4, free T4, T3), prolactin, PSA or Hgb A1C between silodosin and placebo groups.

In study SI04011, there was no significant mean change from baseline up to week 40/end of treatment in PSA or serum thyroid parameters. Prolactin and HgbA1C were not measured in this trial.

A greater percentage of silodosin subjects than those on placebo experienced shifts from normal at baseline to high at week 12/LOCF in HgbA1C– 4.5% (21/466) versus 1.8% (8/457), respectively.

7.1.5.2.3.1 Other Laboratory Outliers: HgbA1C

In the 74-day letter to the sponsor, DRUP stated that the clinical significance of a greater number of silodosin subjects experiencing a shift from normal to high in HgbA1C was unclear but would be a review issue. In response, the sponsor submitted a white paper on the effect of silodosin on HgbA1C (ser 005, 6/3/08). The paper contains a summary of HgbA1C data from the two controlled Phase 3 trials, as well as line listings for subjects experiencing a shift from normal to high in HgbA1C.

In both controlled Phase 3 studies, the mean and median HgbA1C values and change from baseline HgbA1C values are nearly identical for the silodosin and placebo groups (see Tables 7.7 and 7.8).

Table 7.7 Mean HgbA1C values at baseline and end-of-treatment (safety population), Phase 3 trials SI04009 and SI04010

Study	Visit	Statistic	Placebo	Silodosin
SI04009	**Baseline**	Mean (SD)	5.7 (0.57)	5.7 (0.53)
		Median	5.7	5.65
		N	220	219
	Week 12/ET	Mean (SD)	5.8 (0.54)	5.8 (0.56)
		Median	5.8	5.7
		N	220	220
SI04010	**Baseline**	Mean (SD)	5.7 (0.39)	5.7 (0.40)
		Median	5.7	5.7
		N	221	229
	Week 12/ET	Mean (SD)	5.8 (0.69)	5.8 (0.46
		Median	5.8	5.8
		N	219	226

Source: NDA 22-206 ser 005, section 5.3.5.3.3

Table 7.8 Change from baseline in HgbA1C (safety population), Phase 3 trials SI04009 and SI04010

Study	Visit	Statistic	Placebo	Silodosin
SI04009	Week 12/ET	Mean (SD)	0.1 (0.25)	0.1 (0.23)
		Median	0.1	0.1
		N	212	208
SI04010	Week 12/ET	Mean (SD)	0.1 (0.24)	0.1 (0.22)
		Median	0.1	0.1
		N	212	223

Source: NDA 22-206 ser 005, section 5.3.5.3.3, silodosin effects on HgbA1C

In the European Phase 3 trial, there was no significant difference in the mean change from baseline to week 12 in HgbA1C between silodosin and placebo-treated subjects.

Among subjects who experienced a shift in HgbA1C from normal at baseline to high at week 12/ET, the magnitude of the shift was greater in the placebo group (Table 7.9). Mean HgbA1C values for subjects experiencing a shift are shown in Table 7.19.

Table 7.9 Change from baseline in HgbA1C (outlier population)

Visit	Statistic	Placebo N=8	Silodosin N=21
Week 12/ET	Mean (SD)	0.75 (0.5)	0.47 (0.35)
	Median	0.6	0.4
	N	8	21

Table 7.10 Mean HgbA1C at baseline and end-of-treatment (outlier population)

Visit	Statistic	Placebo	Silodosin
Baseline	Mean (SD)	6.3 (0.16)	6.3 (0.14)
	Median	6.35	6.3
Week 12/ET	Mean (SD)	7.0 (0.5)	6.7 (0.3)
	Median	6.95	6.6

Reviewer's comment: The prevalence of diabetes among patients experiencing a shift in HgbA1C from normal to high was similar in the silodosin and placebo groups. Of the 21 silodosin patients, five had a pre-existing history of diabetes mellitus. Of the 8 placebo subjects, three had a known history of diabetes.

The effect of silodosin on glycemic control in patients with pre-existing diabetes was examined by this reviewer. A similar number of diabetics were randomized to silodosin and placebo groups in both studies.

Although the mean change from baseline in the silodosin group was greater than in the placebo group, the mean change in the placebo group was driven largely by one subject who experienced a significant decrease in HgbA1C. The median change was similar in the two groups (Table 7.11).

Table 7.11 Change from baseline in HgbA1C (Diabetic Patients)

Visit	Statistic	Placebo N=24	Silodosin N=25
Week 12/ET	Mean (SD)	0.03 (0.48)	0.3 (0.45)
	Median	0.1	0.2
	N	23	25

The sponsor concluded that the data do not suggest that the use of silodosin caused any meaningful affect on HgbA1C.

This reviewer agrees with the sponsor's assessment for the following reasons:

1) *the mean and median change from baseline in HgbA1C was identical in placebo and silodosin groups in both Phase 3 trials.*
2) *among patients who experienced a shift outside of the normal range, the mean and median size of the shift was larger in the placebo group.*
3) *There was no clinically meaningful change in HgbA1C in diabetic patients assigned to silodosin. In addition, the median change from baseline in HgbA1C was nearly identical in diabetics in the placebo and silodosin groups.*

7.1.6 Special Safety Signals – Liver Function Tests

U.S. Safety Database (Placebo-Controlled)
Line listings from controlled Phase 3 studies SI04009 and SI04010 were searched for subjects with a post-treatment AST or ALT value >3-5 X ULN, >5X ULN or >10X ULN, GGT>2X ULN or a total bilirubin value >2X ULN. Results are shown in Table 7.12, and the narratives for silodosin subjects who met any of these criteria follow.

Table 7.12 Subjects meeting pre-specified criteria for abnormal liver function test, U.S. Controlled Phase 3 Studies (Safety Population)

Analyte	Degree above upper limit of normal	Silodosin N=457	Placebo N=466
AST (0-37 U/L)	3-5X ULN	0	0
	>5X ULN	1	0
	>10X ULN	0	0
ALT (0-47 U/L)	3-5X ULN	0	0
	>5X ULN	0	0
	>10X ULN	0	0
GGT (0-51 U/L)	>2XULN	1	1
T.Bili 0-1.1 ug/dL)	>2X ULN	2	1

Source: NDA 22-206 Ser 005, section 5.3.5.3.3, silodosin effects on liver function tests

No subjects had abnormal liver function tests that met Hy's law criteria (transaminase >3X ULN combined with increased bilirubin to at least 2X ULN)[5] at any point during the trial.

> *Patient 114034* This patient had a history of arthritis, hyperlipidemia, hypertension, cardiomyopathy, inguinal hernia, cholecystectomy, colon polyps, a cardiac stent, and BPH. Concomitant medications were lisinopril 40 mg qd, atorvastatin 20 mg qd, aspirin 325 mg qd, thiamine 100 mg qd, folic acid 400 mcg qd, niacin 25 mg qd, omega 3 and fish oil. The patient was randomized to silodosin on 18 Nov 2005 and received silodosin for 141 days. He completed study SI04009 and entered into the open-label study SI04011, but discontinued early due to patient reported lack of efficacy. Last dose of silodosin was on April 7, 2006. Time course of LFTs for this patient is presented in Figure 7.2.

[5] Temple, Robert. Hy's law: predicting serious hepatotoxicity. Pharmacoepi and Drug Safety 2006; 15: 241-243.

Figure 7.2 Laboratory Values, Patient 114034

Lab/Date	29 Sep 05	17 Oct 05	31 Oct 05	16 Dec 05	13 Feb 06	15 Mar 06	7 Apr 06
Visit	Scr	V1	unsc	V7	V8	unsc	unsc
ALT	26	29	31	n/a	46	**69**	38
AST	16	22	23	n/a	34	**218**	24
GGT	48	**53**	**57**	n/a	48	**120**	**60**
LDH	148	157	152	n/a	205	246	183
Bilirubin	**1.3**	1.1	**1.4**	n/a	**2.0**	0.6	**2.0**

n/a = not available; Scr = Screening Visit; unsc = unscheduled
Shaded cells are out-of-range; red is >3xULN
Bold vertical bar represents end of placebo lead-in and start of silodosin therapy

Source: NDA 22-206 ser 0005, submitted 6/3/08.

The sponsor believes that the return of transaminase values to normal despite continuation of silodosin treatment suggest that the event was unrelated to silodosin use. The sponsor suggests that a sub-acute myocardial infarction may have caused the transient elevation in ALT and AST.

Reviewer's comment: Negative re-challenge suggests that silodosin was not responsible for transaminase elevation.

Patient 114070 was a 53-year-old white male with a history of BPH, type II diabetes, and arthritis of the shoulders. Concomitant medications were insulin, diclofenac and vitamins. He completed study SI04009 but did not enter into the open-label study SI04011. The patient was randomized to silodosin on March 15, 2006, and received silodosin for 90 days (discontinued on 6/12/06). The time course for his LFTs is presented in Table 7.13.

Table 7.13 LFTs, Subject 114070

	2/1/06	2/15/06	3/6/06	4/12/06	6/12/06
Visit	Scr	V1	uns	V7	V8
ALT	23	34	25	58	46
AST	29	42	32	90	48
GGT	72	101	70	151	754
LDH	180	178	153	194	186
Bilirubin	0.4	0.4	0.3	0.8	0.5

Source: NDA 22-206 ser 005

The investigator provided no comments on the laboratory findings.

The sponsor noted that the elevation in AST and GGT began prior to initiation of silodosin therapy, suggesting an alternative cause for liver dysfunction.

Reviewer's comment: This reviewer agrees with the sponsor's assessment and believes that silodosin is unrelated to abnormal liver function tests in this patient.

Two silodosin subjects (pt #250024 and #121002) experienced an increase in total bilirubin to >2X ULN during the study. However, both subjects had elevated total bilirubin at screening (2.0 mg/dl in each subject). Peak total bilirubin was 2.5 mg/dl (subject 250024) and 2.8 mg/dL (subject 121002). Neither subject experienced an increase in serum transaminase or GGT. These laboratory abnormalities are not considered clinically significant by this reviewer.

U.S. Safety Database (Open-Label)

Safety data from study SI04011 was searched subjects meeting the following criteria: AST or ALT >3-5 X ULN, >5X ULN or >10X ULN, GGT>2X ULN or a total bilirubin value >2X ULN. Results are shown in Table 7.14 and the narratives for silodosin subjects who met any of these criteria follow.

Table 7.14 Subjects meeting pre-specified criteria for abnormal liver function test, U.S. Open-Label Safety Extension Study (SI04011)

Analyte	Degree above upper limit of normal	Silodosin N=661
AST (0-37 U/L)	3-5X ULN	2
	>5X ULN	1
	>10X ULN	0
ALT (0-47 U/L)	3-5X ULN	2
	>5X ULN	0
	>10X ULN	0
T.Bili 0-1.1 ug/dL)	>2X ULN	2

LFTs for each patient meeting these criteria are shown in Table 7.15.

Table 7.15 LFTs for subjects meeting pre-specified abnormal criteria, U.S. Open-label safety extension study (SI04011)

	AST	ALT	GGT	TBili
101021				
Screening (8/9/05)	42	56	**91**	0.3
Visit 11 (2/8/06)	**124**	**104**	**81**	0.3
ET (6/2/06)	31	38	**74**	0.3
122046				
Screening (1/17/06)	38	43	42	0.6
ET (8/29/06)	**156**	**151**	**96**	0.7
125001				
Screening (6/20/05)	19	35	57	0.8
ET (7/27/06)	60	**173**	**243**	0.6
ET (8/1/06)	42	**143**	**254**	0.6
268038				
Screening (11/28/05)	19	19	22	0.6
ET (10/4/06)	**127**	**82**	21	0.5