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RESEARCH**

APPLICATION NUMBER:
NDA 22-206

SUMMARY REVIEW

**Office Decisional Memorandum
Rapaflo (silodosin)**

Date: October 10, 2008
From: Daniel A. Shames MD
Deputy Director, Office of Drug Evaluation III (ODE III)
CDER/FDA
To: File

Identifying Information

NDA #: 22-206
Applicant: Watson Laboratories, INC
Product name: silodosin
Proposed Trade Name: Rapaflo
Submission date: December 11, 2008
PDUFA goal date: October 11, 2008
Formulation: 4 and 8mg capsules
Proposed regimen: 8 mg orally once daily

Indication (BPH) Treatment of signs and symptoms of benign prostatic hypertrophy
Intended population: Adult men
Regulatory Decision: Approval

This communication summarizes the key issues related to the decision to approve this application and its associated labeling. A more detailed summary of these issues can be found in the review of Dr George Benson who was the cross-discipline team leader (CDTL) for this project. The form and content of my review are based in large part on the Reviews of Drs. Benson and Olivia Easley, the primary medical reviewer. Further in-depth review and analysis of the specific issues can be found in the primary reviews of the listed individuals. This decisional review contains my summary, assessment and conclusions regarding the major issues found in this original New Drug Application (NDA) for Rapaflo (silodosin).

The primary disciplines have all written review documents for this NDA submission, which should be consulted for more specific details. The primary review documents include the following:

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

1.0 Background

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

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®).

There are currently three identified α -1-receptor subtypes (α 1A, α 1b and α 1d). All three subtypes exist in a wide range of human tissues, including the systemic vasculature, the prostatic smooth muscle and bladder neck. The α 1A 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.

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).

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.

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

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.,

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

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 (Q_{max}) was a co-primary endpoint in the Phase 2 trial and a pre-specified secondary endpoint in the two Phase 3 studies.

2.0 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.

Efficacy results from each individual trial are shown in Table 1

Table 1 Placebo-subtracted mean change from baseline to endpoint/LOCF in IPSS and Q_{max}.

	<u>U.S. controlled Phase 2/3 trials</u>		
	1D-3213-US012-99 (N=90)	SI04009 (N=233)	SI04010 (N=233)
	-2.8	-2.9	-2.9
p-value	0.0018	<0.001	<0.001
	+1.9	+1.0	+1.0
p-value	0.0174	0.0060	0.0431

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 Q_{max} of 1.1 ml/sec (p=0.0002) from baseline to endpoint (LOCF).
- These results are considered clinically meaningful

3.0 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.

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, seventeen serious adverse events (SAEs) were reported in 13 patients (6 on silodosin, 7 on placebo) during the double-blind treatment period. No SAEs were reported in the United States controlled Phase 2 study.

Narratives for all SAEs were reviewed by the primary medical officer. Only the one case of syncope appeared to be possibly related to study drug.

Narrative summaries of the SAEs from the open label extension trial were reviewed by the primary medical officer. A relationship to silodosin could be reasonably excluded in nearly all cases except that of one 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 2.

Table 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 extension trial, 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:

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

Table 3. Treatment-emergent adverse events that occurred in $\geq 2\%$ of patients receiving silodosin in Phase 3 controlled 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.

3.1 Special Safety Issues

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 4).

Table 4 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%)

The issues of hepatic and renal safety will be discussed in sections 3.11 and 3.12

3.11 Hepatic Safety

Line listings from the two controlled Phase 3 studies 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 5.

Table 5. 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 Clinical Review Team and the relationship to silodosin use was deemed unlikely. The Team further concluded that Data from controlled clinical trials do not suggest that silodosin has a clinically meaningful adverse effect on hepatic function. I agree with their assessment.

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 were reviewed by the Clinical Team and Division of Pharmacovigilance. The analyses of these cases were as follows:

- 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.

The Review Team concluded that evidence from the clinical trials and post-marketing reports, is not convincing that silodosin adversely effects hepatic function. However, the Team believes 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. I agree with this plan.

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3.12 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 Clinical Team that, based on the available data, silodosin has no meaningful effect on serum creatinine.

3.2 Other Notable Safety Issues

3.21 QT

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 Clinical Team and the IRT/QT consultant that there are no data which implicate silodosin with prolongation of the QT interval.

3.22 Co administration 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. 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. 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.

However, the Clinical Team 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 comorbidities 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.

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- This small study does not support _____

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I agree with the Medical Team's conclusion and recommendations.

3.23 Hgb A1C

In the 74-day letter to the Sponsor, The Division of Reproductive and Urologic Products stated that the clinical significance of the greater number of silodosin subjects compared to placebo 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 (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.

The Review Team agreed with the Sponsor that the data do not suggest that the use of silodosin caused any meaningful affect on HgbA1C. The Review Team agreed with Sponsor for the following reasons:

- The mean and median change from baseline in HgbA1C was identical in placebo and silodosin groups in both Phase 3 trials.
- 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.
- 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.

I agree with the Review Teams conclusions

3.3 Safety Summary:

I agree with the following conclusions reached by the Review Team

- 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.

4.0 Clinical Pharmacology Issues

4.1 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.

4.2 Cytochrome P450 3A4 (CYP3A4), P-glycoprotein (P-gp) and Related Drug Interaction Issues

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 Review Team that strong CYP3A4 inhibitors should be contraindicated in patients taking silodosin. _____

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It should be noted that 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 $T_{1/2}$ 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 metabolic effects of ketoconazole is not possible at this time. Because of the risk of hypotension, however, I agree with Review Team 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 further agree with the Review Team that “caution should be exercised” when co-administering silodosin with moderate CYP3A4 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. I agree with the Review Team that silodosin should not be used concomitantly with strong P-gp inhibitors (e.g. cyclosporine or itraconazole).

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

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.

4.3 Use in 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).

Based on these data the Review Team recommended 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. I agree with these assessments and recommendations.

4.4 Hepatic Insufficiency: Silodosin exposure did not increase 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 by the Review Team in subjects with mild or moderate hepatic impairment.

Silodosin has not been studied in patients with severe hepatic impairment (Child-Pugh score ≥ 10) and therefore the Review Team does not recommend silodosin's use in this population.

I agree with these recommendations.

5.0 Conclusions and Regulatory Action

I agree with the recommendation of the Review Team 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.

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.

The Review Team suggests the following be specified in the product Approval Letter:

- a. 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.
- b. The sponsor should obtain comprehensive follow-up of all expedited reports of serious hepatic adverse events.”

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

I will communicate the Approval action to the Sponsor in a regulatory letter.

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/s/

Daniel A. Shames
10/8/2008 01:53:35 PM
MEDICAL OFFICER
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