New Drug

Silodosin: A Selective α_{1A}-Adrenergic Receptor Antagonist for the Treatment of Benign Prostatic Hyperplasia

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ABSTRACT

Background: Silodosin is a new α_1-adrenergic receptor antagonist that is selective for the α_{1A}-adrenergic receptor. It was approved by the US Food and Drug Administration (FDA) in 2008 for the treatment of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

Objective: This article reviews the pharmacology, pharmacokinetics, clinical efficacy, adverse effects, drug interactions, and dosage and administration of silodosin in adult male patients with BPH.

Methods: A search of MEDLINE (1950–October 8, 2009), International Pharmaceutical Abstracts (1970–October 8, 2009), and the Iowa Drug Information Service database (1966–October 8, 2009) was conducted using the terms *silodosin*, *KMD-3213*, *benign prostatic hyperplasia*, and *α_1-adrenergic receptor antagonist*. Reports of research and review articles published in English were identified and evaluated, and the bibliographies of these articles were reviewed for additional relevant publications. A search of the FDA Web site was performed, and abstracts and posters presented at scientific meetings of the American Urological Association were reviewed.

Results: By antagonizing α_{1A}-adrenergic receptors in the prostate and urethra, silodosin causes smooth muscle relaxation in the LUT. Silodosin has greater affinity for the α_{1A}-adrenergic receptor than for the α_{1B}-adrenergic receptor (by a factor of 583), minimizing the propensity for blood pressure–related adverse effects mediated by α_{1B} blockade. In 3 controlled clinical studies in patients with BPH-related LUTS (1 published; 2 presented in the prescribing information and published in a pooled analysis), patients receiving silodosin at a total daily dose of 8 mg had significant improvements in the International Prostate Symptom Score (IPSS) and maximum urinary flow rate (Q_{max}) compared with those receiving placebo (both, $P < 0.05$). The most commonly reported adverse effect was abnormal or retrograde ejaculation (>22%), and the incidence of orthostatic hypotension was low (<3%).

Conclusions: In the small number of clinical trials reviewed, silodosin was associated with significant reductions in IPSS and Q_{max} compared with placebo. To determine whether silodosin's selectivity for the α_{1A}-adrenergic receptor translates into a clinical advantage relative to other available agents, long-term studies evaluating the comparative efficacy and tolerability of silodosin and other α_1-blockers (specifically tamsulosin) are necessary. (*Clin Ther.* 2009;31:2489–2502) © 2009 Excerpta Medica Inc.

Key words: silodosin, KMD-3213, benign prostatic hyperplasia, α_{1A}-adrenergic receptor antagonist, α-blocker, selective.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common progressive disease among men, with an incidence that is age dependent. Histologic BPH, which typically develops after the age of 40 years, ranges in prevalence from >50% at 60 years to as high as 90% by 85 years.[1–3] BPH contributes to, but is not the single cause of, bothersome lower urinary tract symptoms (LUTS) that may affect quality of life (QoL).

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The prevalence of troublesome symptoms increases with age, with symptoms typically occurring in men aged ≥50 years.[3]

Histologically, BPH is characterized by a progressive increase in the number of epithelial and stromal cells that develops initially in the periurethral area of the prostate gland.[1,4,5] This cellular proliferative process increases prostatic smooth muscle tone, resulting in urethral constriction.[6] Benign prostatic enlargement (BPE) may also result from the proliferation of epithelial and stromal cells and may further contribute to constriction of the urethra, leading to bladder outlet obstruction (BOO). BPE and BOO do not occur in all men with histopathologic BPH/LUTS, and the presence of BPE does not necessarily mean that BOO will develop.[5]

Approximately 50% of patients with histologic BPH report moderate to severe LUTS,[2] consisting of storage and voiding symptoms.[2,3] Commonly reported storage-related symptoms include urinary frequency, urgency, and nocturia. Voiding symptoms, typically attributable to urethral obstruction, consist of decreased and intermittent force of the urinary stream and the sensation of incomplete bladder emptying.[1] Although bothersome LUTS may affect QoL by altering normal daily activities and sleep patterns, mortality associated with BPH is rare.[1,7] Although uncommon, serious complications of BPH may occur, including acute urinary retention, renal insufficiency, urinary tract infection, hematuria, bladder stones, and renal failure.[6,8] These complications may be triggered or worsened by inadequate management of BPH. The incidence of acute urinary retention in untreated patients ranges from 0.3% to 3.5% per year; the risk of developing other long-term complications is unclear.[8]

The management of patients with BPH includes nonpharmacologic, pharmacologic, and procedural/surgical options, with the choice of therapy typically depending on the presence and severity of symptoms.[1,9] Watchful waiting is the preferred management strategy for patients with mild LUTS and those who do not perceive their symptoms to be particularly bothersome. Pharmacologic treatments include α_1-adrenergic receptor (AR) antagonists (or blockers) and 5α-reductase inhibitors, which are recommended for use alone or in combination in patients with bothersome moderate to severe LUTS. Treatment with 5α-reductase inhibitors is reserved for those with demonstrated prostatic enlargement.[1,9] Minimally invasive procedures such as transurethral needle ablation of the prostate, an outpatient procedure, are alternative options for men with mild to moderate[9] or severe symptoms.[1] Patients presenting with severe symptoms of BPH may undergo surgical procedures such as transurethral resection of the prostate or transurethral incision of the prostate.

Therapy with α_1-blockers generally leads to rapid improvement in LUTS; thus, these agents are commonly used as first-line treatments for LUTS associated with BPH.[3,6] A number of α_1-blockers (alfuzosin, doxazosin, tamsulosin, terazosin) have been approved for the treatment of BPH in the United States; of these, tamsulosin is selective for the α_{1A}-AR. In patients with BPH-related LUTS, α_1-blockers relax prostate smooth muscle and decrease urethral resistance, thereby relieving LUTS[9] and BOO.[10] According to the American Urological Association (AUA) Practice Guidelines Committee,[1] these agents have comparable clinical effectiveness, although differences in their pharmacologic profiles imply differences in their adverse-effect profiles. The greatest safety concern associated with the use of these agents is the occurrence of vasodilatory symptoms such as dizziness and orthostatic hypotension resulting from inhibition of α_1-ARs in the systemic vasculature; this effect is minimized by use of agents that selectively antagonize the α_{1A}-AR.[7]

In October 2008, the US Food and Drug Administration (FDA) approved the α_1-AR antagonist silodosin* for the treatment of the signs and symptoms of BPH.[11] Silodosin is selective for the α_{1A}-AR, making it the second selective agent in its class. The present article reviews the pharmacology, pharmacokinetics, clinical efficacy, adverse effects, drug interactions, and dosage and administration of silodosin in adult male patients with BPH.

METHODS

A literature search of MEDLINE (1950–October 8, 2009), International Pharmaceutical Abstracts (1970–October 8, 2009), and the Iowa Drug Information Service database (1966–October 8, 2009) was conducted with the search terms *silodosin*, *KMD-3213*, *benign prostatic hyperplasia*, and *α_1-adrenergic receptor antagonist*. Original research articles and review arti-

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cles in English were identified and evaluated, and the bibliographies of these articles were reviewed for additional pertinent publications. A search of the FDA Web site was performed using the same search terms. Abstracts and posters presented at scientific meetings of the AUA through April 2009 were also reviewed.

CLINICAL PHARMACOLOGY

The chemical formulation of silodosin is 1-(3-hydroxypropyl)-5-[(2R)-2-({2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl}amino)propyl]-2,3-dihydro-1*H*-indole-7-carboxamide (KMD-3213).[11] The compound has a molecular weight of 495.53 and a molecular formula of $C_{25}H_{32}F_3N_3O_4$. The chemical structure of silodosin is shown in the **figure**.

MECHANISM OF ACTION

α_1-ARs have been identified in a wide range of human tissues[10] and are abundant in the smooth muscle of the prostate.[12,13] To date, 3 unique α_1-AR subtypes (α_{1A}, α_{1B}, and α_{1D}) have been identified.[6,10,14] While there are data indicating the existence of a fourth α_1-AR subtype (α_{1L}), its role has yet to be established.[13,15] The α_1-ARs are members of the larger family of G protein–coupled receptors that act indirectly through guanine nucleotide proteins and various second-messenger molecules.[12] After binding to epinephrine and norepinephrine,[14] α_1-ARs undergo a process that includes phospholipase C activation and generation of the second messengers inositol triphosphate and diacylglycerol, ultimately resulting in increased intracellular calcium levels and smooth muscle contraction.[12,14]

The α_{1A}-AR subtype predominates in the human prostate and urethra. Cloning and messenger RNA assays have indicated that 69.3%, 3.3%, and 27.3% of α_1-ARs in the human prostate are subtypes α_{1A}, α_{1B}, and α_{1D}, respectively.[12,13] The distribution appears to change in the prostate tissue of patients with BPH, with the α_{1A} and α_{1D} subtypes accounting for a respective 85% and 14% of α_1-ARs, and α_{1B}-AR expression becoming negligible.[12,13] In patients with symptomatic BPH, therefore, blockade of the α_{1A}-AR is responsible for relaxation of the prostate smooth muscle and an increase in urine flow.[10,12] The α_{1D}-AR subtype is expressed mainly in the detrusor muscle of the bladder and the sacral region of the spinal cord[6,14]; recent data suggest that blockade of this AR subtype yields relief of bladder symptoms through direct activity on the bladder and/or spinal cord reflexes.[10] On the other hand, the α_{1B}-AR subtype is expressed in the peripheral vasculature and is important in the regulation of blood pressure, specifically in older individuals; blockade of α_{1B}-ARs has no utility in the treatment of BPH-related LUTS.[6,14]

Shibata et al[16] examined the binding affinity of silodosin to cloned human α_1-AR subtypes in an in vitro study using Chinese hamster ovary cells (**Table I**). Silodosin's affinity for the α_{1A}-AR subtype was 583-fold that for the α_{1B}-AR and 56-fold that for the α_{1D}-AR, indicating its selectivity for the α_{1A}-AR. As indicated by its lower dissociation constant values, tamsulosin's affinity for each α_1-AR subtype was greater than that of silodosin. The selectivity ratio indicated that tamsulosin was 15- and 3-fold more selective for the α_{1A}-AR than for the α_{1B}- and α_{1D}-AR subtypes, respectively. Thus, although tamsulosin's affinity for the α_{1A}-AR subtype was greater than that of silodosin, silodosin's selectivity for the α_{1A}-AR over the α_{1B}- and α_{1D}-AR subtypes exceeded that of tamsulosin.

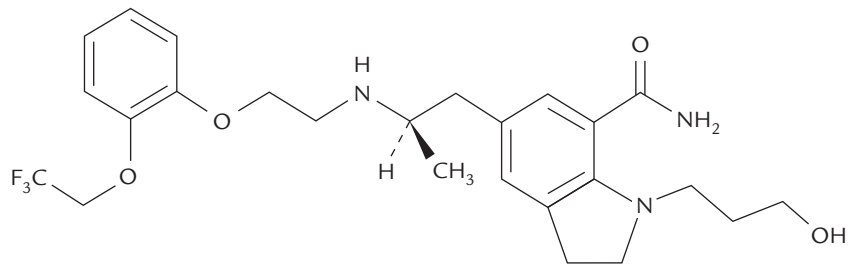

Figure. Chemical structure of silodosin.[11]

Table I. Affinity (dissociation constant [K_i]) and selectivity of silodosin and tamsulosin for cloned human α_1-adrenergic receptor (α_1-AR) subtypes in cultured Chinese hamster ovary cells.[16]

	K_i, Mean (SE), nM*			α_1-AR Subtype Selectivity Ratio	
Drug	α_{1A}-AR	α_{1B}-AR	α_{1D}-AR	α_{1A}/α_{1B}	α_{1A}/α_{1D}
Silodosin	0.036 (0.010)	21 (5)	2.0 (0.4)	583	56
Tamsulosin	0.019 (0.002)	0.29 (0.02)	0.063 (0.011)	15	3

*Each value represents the mean of 3 to 5 different experiments.

Silodosin's "uroselectivity" (ie, selectivity for the human prostate) has been found to be ~200-fold higher than its selectively for the aorta.[15] In comparison, tamsulosin's selectivity for prostatic tissue exceeds its selectivity for the aorta by a factor of 10.[15] These findings illustrate silodosin's strong affinity for prostatic tissue. Furthermore, although tamsulosin is selective for prostatic tissue, its uroselectivity is less than that of silodosin. Data from preclinical studies conducted in various animal models confirmed silodosin's uroselectivity, albeit to varying degrees (**Table II**).[17–20] In these models, uroselectivity was determined based on the ratio of the dose required to decrease mean blood pressure by either 15% or 20% and the dose required to inhibit intraurethral pressure by 50%. These studies further supported silodosin's greater uroselectivity relative to tamsulosin.

PHARMACOKINETICS

The pharmacokinetics of silodosin are summarized in **Table III**. In dose-ranging studies, the pharmacokinetic parameters of silodosin were found to be linear.[11] The mean (SD) steady state C_{max} and AUC of silodosin 8 mg once daily administered with food in healthy adult volunteers were 61.6 (27.54) ng/mL and 373.4 (164.94) ng · h/mL, respectively. Across 3 studies, administration of silodosin with a moderate-fat, moderate-calorie meal had an inconsistent effect on C_{max} and AUC; these parameters were decreased by ~18% to 43% and ~4% to 49%, respectively.

Silodosin T_{max} occurs at a mean of 2.6 hours after administration.[11] Oral silodosin is ~32% bioavailable. It has an apparent V_d of 49.5 L, and is 97% bound to plasma proteins. Silodosin undergoes extensive metabolism through glucuronidation to its primary metabolite, KMD-3213G. It is also metabolized to KMD-3293 by alcohol and aldehyde dehydrogenase. In addition, silodosin undergoes metabolism through cytochrome P450 (CYP) 3A4 pathways. KMD-3213G has been found to be active in vitro, with an extended $t_{1/2}$ of ~24 hours and an AUC ~4 times that of silodosin. KMD-3293 is not expected to contribute to the overall pharmacologic activity of silodosin. Silodosin has a mean (SD) $t_{1/2}$ of 13.3 (8.07) hours, and is excreted in the urine (33.5%) and feces (54.9%).

Special Populations

The effects of moderate renal impairment on the pharmacokinetics of silodosin were evaluated in a single-dose study in 6 patients with moderate renal impairment (creatinine clearance [CrCl] 30–50 mL/min) and 7 subjects with normal renal function.[11] In the patients with moderate renal impairment, the silodosin AUC, C_{max}, and elimination $t_{1/2}$ were 3.2-, 3.1-, and 2-fold higher, respectively, compared with values in normal controls (statistical analysis not provided). Dose adjustment is recommended in patients with moderate renal insufficiency. Silodosin has not been studied in patients with severe renal insufficiency (CrCl <30 mL/min), and its use is contraindicated in this population.

In a study in 9 patients with moderate hepatic impairment (Child-Pugh score 7–9) and 9 subjects with normal hepatic function, no significant differences in silodosin pharmacokinetics were observed between the 2 groups (data not provided).[11] The pharmacokinetics of silodosin have not been evaluated in patients with severe hepatic impairment (Child-Pugh score ≥10), and its use is contraindicated in these patients.

Table II. Uroselectivity of silodosin and tamsulosin in in vivo animal models.

Experimental Condition	Intraurethral Pressure ID_{50}, μg/kg	Mean Blood Pressure ED_{15}, μg/kg	Uroselectivity Index (ED_{15}/ID_{50})
Rat model[17] (IV administration)			
Silodosin	1.4	80	57
Tamsulosin	0.67	2.7	4.0
Rat model[18] (IV administration)			
Silodosin	1.4	12	8.6
Tamsulosin	0.67	0.70	1.0
Rat model[18] (intraduodenal administration)			
Silodosin	54	870	16.1
Tamsulosin	19	61	3.2
Dog model[19] (IV administration)			
Silodosin	3.15	8.03*	2.55†
Tamsulosin	1.73	0.59*	0.345†
Dog model[19] (intraduodenal administration)			
Silodosin	26.4	>100*	>3.79†
Tamsulosin	5.48	5.95*	1.09†
Dog model[20] (IV administration)			
Silodosin	1.86	440	237
Tamsulosin	0.908	0.837	1.21

ID_{50} = dose required to decrease intraurethral pressure by 50%; ED_{15} = dose required to decrease mean blood pressure by 15%.
*Values are ED_{20}.
†Values are ED_{20}/ID_{50}.

The pharmacokinetics of silodosin have been studied in 12 elderly men (mean age, 69 years) and 9 young men (mean age, 24 years).[11] Compared with values in the younger population, the AUC and elimination $t_{1/2}$ of silodosin in elderly subjects were ~15% and ~20% higher, respectively (statistical analysis not provided). No difference in silodosin C_{max} was observed between the 2 populations. In Phase III clinical studies of silodosin, the incidence of orthostatic hypotension was greater in elderly patients compared with younger ones.[11] Thus, caution may be warranted when prescribing silodosin for the elderly, although no dose adjustment is recommended in the prescribing information.

Silodosin is not indicated for use in women and it has not been studied in patients aged <18 years.[11]

CLINICAL EFFICACY

Four clinical studies (2 published; 2 presented in the silodosin prescribing information and published in a pooled analysis) conducted in Japan and the United States have evaluated the use of silodosin in the treatment of patients with BPH.

Phase III Studies

Kawabe et al[21] conducted a 12-week, multicenter, randomized, double-blind, active- and placebo-controlled, noninferiority/superiority study to evaluate the efficacy and tolerability of silodosin in Japanese men with BPH-related LUTS. Men aged ≥50 years with an International Prostate Symptom Score (IPSS) >8, QoL score >3, prostate volume >20 mL, maximum urinary flow rate (Q_{max}) <15 mL/sec, voided volume >100 mL, and postvoid residual urine volume <100 mL were eligible for enrollment. The IPSS, which is scored from 0 to 35 (0–7 = mild; 8–19 = moderate; 20–35 = severe), consists of 7 questions assessing LUTS and a separate disease-specific QoL question (scored from 0 = delighted to 6 = terrible). After a 7-day washout and a

Table III. Summary of the pharmacokinetic parameters of silodosin.[11]

Parameter	Value
Bioavailability, %	32
T_{max}, h	2.6
C_{max}, ng/mL	61.6
AUC_{ss}, ng · h/mL	373.4
V_d, L	49.5
Protein binding, %	97
Metabolism	Glucuronidation (primary metabolic route), alcohol and aldehyde dehydrogenase, and cytochrome P450 3A4 pathways
Elimination $t_{1/2}$, h	13.3
Excretion	Urine (33.5%) and feces (54.9%)

7-day observation period, patients were randomized to receive silodosin 4 mg PO BID, tamsulosin 0.2 mg PO once daily, or placebo. The primary efficacy end point was the change in total IPSS from baseline. Secondary efficacy variables included the changes from baseline in Q_{max} and subjective symptoms, consisting of the voiding and storage components of the IPSS and the QoL score. All efficacy measures were assessed at the end of the washout period and at weeks 1, 2, 4, 8, and 12. Tolerability was also assessed based on adverse events (AEs), physical examinations, vital signs, and laboratory tests; the frequency of these evaluations was not described.

Four hundred fifty-seven patients were randomized to treatment (176 silodosin, 192 tamsulosin, 89 placebo).[21] One patient who was randomized to the silodosin group was excluded from the analysis due to a protocol violation. The mean (SD) ages of the silodosin, tamsulosin, and placebo groups were 65.4 (7.0), 65.6 (7.0), and 65.0 (6.9) years, respectively. At baseline, the mean total IPSS was 17.1 (5.7), 17.0 (5.7), and 17.1 (6.1) in the respective groups (**Table IV**). The mean Q_{max} was 9.89 (2.72) mL/sec in the silodosin group, 9.43 (2.79) mL/sec in the tamsulosin group, and 9.96 (2.65) mL/sec in the placebo group. The mean QoL score was 4.9, 4.7, and 4.7 in the 3 groups ($P = 0.018$ among groups). Thus, an adjusted analysis by baseline QoL score was used to evaluate the primary end point.

Patients receiving silodosin had a significantly greater reduction in IPSS compared with those receiving placebo ($P < 0.001$) (**Table IV**).[21] This effect became apparent at week 1 and was maintained throughout the 12-week study period. At week 2, the silodosin group had a significantly greater reduction in IPSS than did the tamsulosin group ($P = 0.011$); however, this effect did not continue throughout the study. At study end, the mean (SD) change from baseline in total IPSS in the silodosin, tamsulosin, and placebo groups was –8.3 (6.4), –6.8 (5.7), and –5.3 (6.7), respectively ($P = 0.110$, silodosin vs tamsulosin; $P < 0.001$, silodosin vs placebo). The mean intergroup differences in total IPSS between silodosin and tamsulosin and silodosin and placebo were –1.4 (95% CI, –2.7 to –0.2) and –3.0 (95% CI, –4.6 to –1.3), respectively (both, $P < 0.001$). Silodosin was noninferior to tamsulosin and superior to placebo.

Although all 3 groups had improvements from baseline in Q_{max} at week 12, there were no significant differences in the change in Q_{max} between groups.[21] The authors noted, however, that Q_{max} is dependent on the voided volume that is measured, and some men in the study had differences in voided volume before and after therapy. A subsequent analysis to control for this variable evaluated the change in Q_{max} in patients with <50% change in voided volume after therapy. In this analysis, the improvement from baseline in Q_{max} was significantly greater in the silodosin group compared with the placebo group ($P = 0.005$), with mean (SD) changes from baseline of 1.70 (3.31), 2.60 (3.98), and 0.26 (2.21) mL/sec in the silodosin, tamsulosin, and placebo groups, respectively (**Table V**).

Voiding symptoms (as measured by components of the total IPSS) were significantly improved in the silodosin group compared with the tamsulosin and placebo groups.[21] The mean (SD) changes from baseline in IPSS subscores were –5.8 (4.6), –4.8 (4.1), and –3.8 (4.8) in the silodosin, tamsulosin, and placebo groups, respectively ($P = 0.023$, silodosin vs tamsulosin; $P < 0.001$, silodosin vs placebo). Mean changes from baseline in storage symptoms were –2.5 (2.9), –2.1 (2.6), and –1.5 (2.6) in the respective groups ($P < 0.006$, silodosin vs placebo; P = NS, silodosin vs tamsulosin). At study end, improvements in the adjusted QoL score were greater in patients treated with silodosin compared with those who received placebo ($P = 0.002$).

Table IV. Changes in total International Prostate Symptom Score (IPSS) from baseline to week 12 in controlled Phase III trials of silodosin.

Study	No. of Patients	IPSS, Mean (SD)	
		Baseline	Change at Study End
Kawabe et al[21]			
Silodosin 4 mg BID	175	17.1 (5.7)	–8.3 (6.4)*
Tamsulosin 0.2 mg once daily	192	17.0 (5.7)	–6.8 (5.7)
Placebo	89	17.1 (6.1)	–5.3 (6.7)
US study 1[11]			
Silodosin 8 mg once daily	233	21.5 (5.38)	–6.5 (6.73)*
Placebo	228	21.4 (4.91)	–3.6 (5.85)
US study 2[11]			
Silodosin 8 mg once daily	233	21.2 (4.88)	–6.3 (6.54)*
Placebo	229	21.2 (4.92)	–3.4 (5.83)
Marks et al[23] (pooled US studies 1 and 2)			
Silodosin 8 mg once daily	466	21.3 (5.1)	–6.4 (6.63)*
Placebo	457	21.3 (4.9)	–3.5 (5.84)

*$P < 0.001$ versus placebo.

The silodosin group had significant improvements in IPSS compared with the placebo group both in patients with moderate symptoms at baseline ($P = 0.001$) and in those with severe symptoms at baseline ($P = 0.044$).

The incidence of AEs in this study was 88.6%, 82.3%, and 71.6% in the silodosin, tamsulosin, and placebo groups, respectively.[21] AEs occurred significantly more frequently in patients who received silodosin compared with placebo ($P < 0.001$; comparison with tamsulosin not provided). In the respective groups, 69.7%, 47.4%, and 36.4% of AEs were considered drug related, with these AEs occurring more frequently in the silodosin group than in the other 2 groups (both comparisons, $P < 0.001$). Withdrawal due to AEs occurred in 18 (10.3%), 11 (5.7%), and 4 patients (4.5%) in the 3 groups. The most common AE in the silodosin group was abnormal ejaculation, which occurred in 39 patients (22.3%), compared with 3 (1.6%) in the tamsulosin group and 0 in the placebo group. Other AEs occurring in the silodosin group at a frequency >5% and more frequently than in the placebo group included upper respiratory tract infection (18.9% silodosin, 27.6% tamsulosin, and 0% placebo), thirst (10.3%, 3.6%, and 4.5%, respectively), loose stool (9.1%, 3.6%, and 5.6%), diarrhea (6.9%, 6.8%, and 5.6%), urinary incontinence (6.3%, 5.7%, and 0%), and dizziness (5.1%, 7.3%, and 4.5%). No statistical analysis of the incidence of AEs was reported.

The following changes in laboratory parameters occurred with an incidence of >5% in the silodosin group and with a greater frequency than in the placebo group: elevated triglycerides (25.1% silodosin vs 20.5% placebo), elevated γ-glutamyl transpeptidase (7.4% vs 6.8%, respectively), and elevated total cholesterol (5.1% vs 2.3%) (statistical analysis not provided).[21] No cardiovascular AEs were reported in the 3 groups, and there were no clinically significant differences between silodosin and tamsulosin with respect to blood pressure or heart rate.

Takao et al[22] conducted a 28-day, open-label, uncontrolled study to evaluate the efficacy of silodosin 4 mg PO BID during the early stages of treatment. Eligible patients were aged ≥45 years, had LUTS suggestive of BPH in their physician's judgment, and had an

Table V. Changes in maximum urinary flow rate (Q_{max}) from baseline to week 12 in controlled Phase III trials of silodosin.

Study	No. of Patients	Q_{max}, Mean (SD), mL/sec	
		Baseline	Change at Study End
Kawabe et al[21]*			
Silodosin 4 mg BID	NR	9.88 (2.75)	1.70 (3.31)†
Tamsulosin 0.2 mg once daily	NR	9.41 (2.81)	2.60 (3.98)
Placebo	NR	10.18 (2.72)	0.26 (2.21)
US study 1[11]			
Silodosin 8 mg once daily	233	9.0 (2.60)	2.2 (4.31)‡
Placebo	228	9.0 (2.85)	1.2 (3.81)
US study 2[11]			
Silodosin 8 mg once daily	233	8.4 (2.48)	2.9 (4.53)§
Placebo	229	8.7 (2.67)	1.9 (4.82)
Marks et al[23] (pooled US studies 1 and 2)			
Silodosin 8 mg once daily	466	8.7 (2.60)	2.6 (4.43)‖
Placebo	457	8.9 (2.80)	1.5 (4.36)

NR = not reported.
*Values are from a subgroup analysis in patients who had <50% change in voided volume before and after treatment.
† $P = 0.005$ versus placebo in post hoc analysis.
‡ $P = 0.006$ versus placebo.
§ $P = 0.043$ versus placebo.
‖ $P < 0.001$ versus placebo.

IPSS ≥8 and QoL index ≥2. The IPSS used in this study was modified from its original version, in that the phrase "over the past month" was removed. QoL was scored as described previously. Those receiving other α_1-blockers underwent a washout of these agents at least 1 week before initiation of silodosin therapy. Efficacy end points included changes in IPSS and QoL index at days 1, 2, 3, 4, 5, 6, 7, 14, and 28. IPSS subscores were evaluated for changes in subjective symptoms. Total IPSS were analyzed on days 3, 7, and 28 to examine the early ability to predict efficacy. All new AEs were recorded.

Sixty-eight patients were enrolled in the study (mean [SD] age, 67.5 [8.0] years).[22] At day 1, the mean IPSS had decreased from 19.38 (7.46) at baseline to 15.81 (7.40), and the QoL score had decreased from 4.68 (1.07) to 4.22 (1.30) (both, $P < 0.05$). Significant decreases from baseline in total IPSS and QoL scores were maintained at each ensuing assessment (data not provided). Improvements were observed regardless of the severity of total IPSS and QoL scores at baseline. IPSS subscores for voiding, storage, and postmicturition symptoms were significantly decreased, from 8.93 (3.95), 7.97 (3.88), and 2.49 (1.70), respectively, at baseline to 7.28 (4.09), 6.52 (3.47), and 2.02 (1.56) at day 1 (all, $P < 0.05$). These improvements were reported to be significant throughout the study (data not provided).

Patients with ≥25% improvement in total IPSS were classified as *good responders*, and those with <25% improvement were classified as *bad responders*.[22] At day 3, 31 of 68 patients (45.6%) were considered good responders, of whom 25 (80.6%) continued to be good responders at study end. At day 7, 42 patients (61.8%) were good responders; 33 of these patients (78.6%) had maintained a good response at

day 28. Conversely, 37 of 68 patients (54.4%) were poor responders at day 3, and 20 of these patients (54.1%) continued to be poor responders at study end. At day 7, 26 patients (38.2%) were poor responders, of whom 17 (65.4%) remained poor responders at day 28. Therefore, the positive predictive value of a response at days 3 and 7 was 80.6% and 78.6%, respectively, and the negative predictive value at days 3 and 7 was 54.1% and 65.4%.

AEs were documented in 6 patients (8.8%).[22] These events consisted of 2 reports of abnormal ejaculation, 2 reports of diarrhea, 1 report of tinnitus, and 1 report of lightheadedness. All AEs resolved after the discontinuation of silodosin.

Two US clinical studies that evaluated the efficacy and tolerability of silodosin 8 mg PO once daily in men with BPH are described individually in the silodosin package insert[11] and were pooled and reported by Marks et al.[23] Both were 12-week, multicenter, randomized, double-blind, placebo-controlled trials; one of them included pharmacokinetic sampling.[11] The 2 studies enrolled patients aged ≥50 years who had an IPSS ≥13, a Q_{max} between 4 and 15 mL/sec, and a postvoid residual volume of <250 mL.[23] The studies began with a 4-week placebo run-in period; patients with a >30% decrease in IPSS or a >3-mL/sec increase in Q_{max} at the end of this period were excluded from subsequent randomization.[23] As in the Phase III studies described earlier, the primary efficacy end point was the change in IPSS at week 12.[11,23] The secondary efficacy end point was the change in Q_{max} at study end.[23] Additional efficacy assessments included IPSS irritative and obstructive symptom subscores and QoL, the latter assessed using IPSS question 8 (scored separately). IPSS and QoL-related assessments were conducted at baseline and at weeks 0.5, 1, 2, 4, and 12. Q_{max} was measured at baseline, 2 to 6 hours after the first dose, and at weeks 1, 2, 4, and 12. Tolerability was assessed based on AE reports (weeks 1, 2, 4, and 12) and 12-lead ECGs, laboratory tests, vital signs, and physical examinations.

Of the 923 patients enrolled in the 2 studies, 466 received silodosin 8 mg PO once daily with breakfast and 457 received placebo.[23] Participants' demographic characteristics were similar in the 2 studies; most were white (89.3%) and the mean age was ~65 years.[23] Baseline measures were also comparable in the 2 groups, with mean IPSS and Q_{max} of ~21.3 and ~8.8 mL/sec, respectively.[11,23]

In study 1, the mean (SD) baseline IPSS in the silodosin and placebo groups was 21.5 (5.38) and 21.4 (4.91), respectively; at study end, the mean changes were –6.5 (6.73) and –3.6 (5.85) ($P < 0.001$) (**Table IV**).[11] The mean baseline Q_{max} was 9.0 (2.60) and 9.0 (2.85) mL/sec, and the mean changes from baseline were 2.2 (4.31) and 1.2 (3.81) mL/sec ($P = 0.006$) (**Table V**). In study 2, the mean baseline IPSS was 21.2 (4.88) and 21.2 (4.92) in the respective groups; the mean change from baseline was –6.3 (6.54) and –3.4 (5.84) ($P < 0.001$) (**Table IV**). The mean baseline Q_{max} was 8.4 (2.48) and 8.7 (2.67) mL/sec, and the changes from baseline were 2.9 (4.53) and 1.9 (4.82) mL/sec ($P = 0.043$) (**Table V**).

The decrease in mean (SD) total IPSS at the first scheduled observation (3–4 days) was significantly greater in the pooled silodosin group than in the pooled placebo group (–4.2 [5.26] vs –2.3 [4.37], respectively; $P < 0.001$).[23] At week 12, the decrease in mean total IPSS (derived from data for the individual studies) remained significantly greater in the pooled silodosin group than in the pooled placebo group (–6.4 [6.63] vs –3.5 [5.84]; $P < 0.001$). In addition, the increase in mean Q_{max} at the first postbaseline assessment (2–6 hours after the first dose) was significantly greater in the pooled silodosin group than in the pooled placebo group (2.8 [3.44] vs 1.5 [3.76] mL/sec; $P < 0.001$). At study end, the improvement in mean Q_{max} (derived from data for the individual studies) remained significantly greater in the pooled silodosin group than in the pooled placebo group (2.6 [4.43] vs 1.5 [4.36] mL/sec; $P < 0.001$).

In the pooled studies, patients randomized to receive silodosin had significantly greater improvements in the mean (SD) IPSS irritative subscore compared with those who received placebo at both 0.5 week (–1.4 [2.35] vs –0.8 [2.16], respectively; $P < 0.001$) and study end (–2.3 [2.93] vs –1.4 [2.66]; $P < 0.001$).[23] Improvement in the IPSS obstructive subscore was also significantly greater in the pooled silodosin group than in the pooled placebo group at the first postbaseline assessment (–2.8 [3.55] vs –1.4 [2.99]; $P < 0.001$); this improvement was sustained at study end (–4.0 [4.31] vs –2.1 [3.76]; $P < 0.001$). The pooled silodosin group had a numerically greater improvement in QoL compared with the pooled placebo group. At baseline, a respective 6.9% and 7.2% of patients in the silodosin and placebo groups reported that they were "delighted, pleased, or mostly satisfied"

with the prospect of living with their current urinary condition for the rest of their lives; at study end, the proportions had increased to 32.0% and 22.5% (statistical analysis not provided).

In the 2 studies, AEs were reported by numerically more patients receiving silodosin (55.2%) than by those receiving placebo (36.8%) (statistical analysis not provided).[11,23] This difference was attributed to the incidence of retrograde ejaculation, which occurred in 28.1% and 0.9% of those receiving silodosin and placebo, respectively.[23] Treatment-emergent orthostatic hypotension occurred in 2.6% of patients treated with silodosin and 1.5% of those who received placebo.[11,23] The incidence of orthostatic hypotension with silodosin increased with increasing age, occurring in 2.3% of silodosin-treated patients aged <65 years (1.2% for placebo), 2.9% of silodosin-treated patients aged >65 years (1.9% for placebo), and 5.0% of silodosin-treated patients aged >75 years (0% for placebo) (statistical analysis not provided).[11] The incidence of dizziness and headache was low; dizziness occurred in 3.2% and 1.1% of patients in the respective groups, and headache occurred in 2.5% and 0.9% (statistical analysis not provided).[23] One serious AE (syncope) occurred in a patient in the silodosin group who was also taking prazosin.[11,23] One case of priapism was reported by a patient receiving silodosin.[11]

ADVERSE EVENTS AND WARNINGS

In the Phase III clinical trials reviewed, a total of 68 patients received silodosin for 28 days[22] and 641 patients received silodosin for 12 weeks.[11,21,23] In controlled clinical trials, the most frequently reported treatment-emergent AEs that occurred more often in the silodosin group than in the placebo group were abnormal or retrograde ejaculation (22.3%–28.1%), upper respiratory tract infection (18.9%), thirst (10.3%), loose stool (9.1%), diarrhea (2.6%–6.9%), urinary incontinence (6.3%), dizziness (3.2%–5.1%), and orthostatic hypotension (2.6%).

Approximately 6.4% to 11.4% of patients discontinued silodosin treatment due to an AE, compared with 2.2% to 8.3% of those assigned to placebo.[11,21,23] Abnormal or retrograde ejaculation was the most common cause of discontinuation of therapy (2.8%–2.9%)[11,21,23]; this effect resolved on discontinuation of silodosin.[11,21] In the clinical trial that contained an active comparator (tamsulosin),[21] the incidence of ejaculatory dysfunction was 22.3% and 1.6% in the respective groups. However, a single-arm meta-analysis conducted by the AUA Practice Guidelines Committee estimated a 10% median rate of ejaculatory disorders with tamsulosin,[1] and additional data suggest that the incidence may be as high as 35.4%.[24,25]

The combined results of an open-label extension of the 2 clinical studies described in the package insert[11] and pooled by Marks et al[23] were summarized in an abstract presented at the 2008 Annual Meeting of the New England section of the AUA.[26] This extension study, which was conducted to determine the long-term tolerability of silodosin, enrolled 661 patients who had successfully completed either of the two 12-week studies described earlier. All patients received silodosin 8 mg PO once daily for 40 weeks. Tolerability evaluations included AEs, vital signs, clinical laboratory tests, ECGs, and physical examinations; the tolerability analysis included all patients who received ≥1 dose of silodosin. Efficacy assessments were based on the IPSS, and the analysis included all patients who completed the study without significant protocol deviations.

Four hundred thirty-five patients (65.8%) completed the extension study.[26] Reasons for discontinuation included AEs (14.1%), lack of efficacy (8.8%), and voluntary withdrawal from the study (5.0%). AEs were reported in 65.2% of the population; 28.4% of patients reported AEs that were considered drug related. AEs and drug-related AEs occurred numerically more frequently in patients who had received placebo in the initial 12-week, double-blind study (71.5% and 37.5%, respectively) compared with those who had received silodosin (58.3% and 18.5%). Although serious AEs occurred in 4% to 5% of patients, none were considered related to therapy. No clinically meaningful changes in blood pressure, clinical laboratory measures, ECGs, or physical examination findings were observed in patients who received silodosin. Retrograde ejaculation was reported by ~20.9% of patients; this led to discontinuation in 7.5% of patients who had previously received placebo and 1.9% of those who had previously received silodosin. In the efficacy population, IPSS decreased by a mean (SD) of 3.1 (6.6) points between weeks 0 and 40. This decrease was greater in patients who had previously received placebo than in those who had previously received silodosin (4.5 [6.7] vs 1.6 [6.0], respectively) (statistical analysis not provided).

One case of intraoperative floppy iris syndrome (IFIS) was reported in a 9-month open-label tolerability study of silodosin.[11] This syndrome, which causes complications of cataract surgery, has been reported in patients being treated with or having previously received α_1-blockers; the association has been strongest with selective blockade of the α_{1A}-adrenoceptor.[27–32] IFIS is characterized by loss of muscle tone in the iris; its clinical manifestations include pupil constriction, fluttering and billowing of the iris stroma, and propensity for iris prolapse during cataract surgery.[27] In a prospective, interventional case series, Oshika et al[33] examined the incidence of IFIS in 1968 Japanese patients undergoing cataract surgery who were receiving various α_1-blockers, including silodosin. The overall incidence of IFIS was 1.1%, although no cases were reported in patients receiving silodosin. However, the number of patients receiving silodosin was not provided. Nonetheless, it is recommended that patients inform their ophthalmologists about silodosin use before undergoing cataract surgery.[11]

Because symptoms of prostate cancer and BPH commonly overlap and the 2 conditions often coexist, it is imperative that prostate cancer be ruled out before the initiation of silodosin therapy.[11]

DRUG INTERACTIONS

The interaction between silodosin and ketoconazole, a strong inhibitor of CYP3A4, was evaluated in a metabolic inhibition study in which a single 8-mg dose of silodosin was coadministered with 400 mg of ketoconazole.[11] The C_{max} and AUC of silodosin increased by 3.8- and 3.2-fold, respectively. Therefore, concomitant administration of silodosin with ketoconazole or other strong CYP3A4 inhibitors (clarithromycin, itraconazole, protease inhibitors) is contraindicated. Although the interaction between silodosin and moderate CYP3A4 inhibitors (diltiazem, erythromycin, verapamil) has not been evaluated, caution should be exercised when these agents are used concurrently.

In vitro studies have found that silodosin is a substrate for P-glycoprotein (Pgp). Therefore, use of silodosin is not recommended in patients taking strong inhibitors of Pgp (cyclosporine), as coadministration may lead to an increase in silodosin concentrations.[11]

A 7-day study in 16 healthy males was conducted to evaluate the potential interaction between silodosin and digoxin, administered at a dose of 0.25 mg/d.[11] Concomitant administration of silodosin and digoxin did not significantly alter the C_{max} or AUC of digoxin; therefore, no dose adjustment is recommended when the 2 agents are coadministered.

Although the potential for interactions between silodosin and other α-blockers has not been evaluated, such interactions may be expected, and silodosin and other α-blockers should not be used concomitantly.[11] Similarly, the potential for interactions between silodosin and antihypertensive agents has not been rigorously assessed in clinical studies. However, the results of US clinical studies of silodosin may shed light on this interaction, as approximately one third of patients in these studies were taking antihypertensive agents. In these studies, patients taking concomitant antihypertensives had a numerically greater frequency of dizziness than did those in the general silodosin population (4.6% vs 3.8%, respectively), as well as a greater frequency of orthostatic hypotension (3.4% vs 3.2%) (*P* value not provided). Although this difference was reported to be nonsignificant, increased monitoring is warranted during concurrent use of silodosin and antihypertensive agents.

The interaction between silodosin and inhibitors of phosphodiesterase type 5 (PDE5) was assessed in a placebo-controlled study in 24 healthy adult males.[11] Silodosin was coadministered with a single dose of sildenafil 100 mg or tadalafil 20 mg. Orthostatic vital signs were monitored for 12 hours after concomitant dosing. During this period, the group who received concomitant therapy had a greater number of positive orthostatic test results compared with those receiving silodosin alone (data not provided). Although symptomatic orthostasis or dizziness was not reported in subjects receiving concomitant therapy, it would be prudent to be alert for this effect during concurrent use of silodosin and a PDE5 inhibitor.

DOSAGE AND ADMINISTRATION

Silodosin is available in the United States as 4- and 8-mg gelatin capsules, and the recommended dose is 8 mg PO once daily.[11] Because clinical studies of silodosin were conducted in the fed state, it is recommended that silodosin be taken with a meal to minimize the risk of AEs. Although dose adjustment is not required in patients with a CrCl >50 mL/min, the dose of silodosin should be decreased to 4 mg once daily in patients with moderate renal impairment. No dose adjustment is required in patients with mild to moderate hepatic impairment. As noted earlier, use of silodosin

is contraindicated in patients with severe renal or hepatic impairment.[11]

PHARMACOECONOMIC CONSIDERATIONS

No cost-effectiveness analyses or other pharmacoeconomic studies of silodosin in the treatment of BPH were identified. The average wholesale price (AWP) of silodosin administered at either 4 or 8 mg/d is $108.72 for a 30-day supply.[34] The monthly acquisition cost of the most commonly prescribed dose of tamsulosin (0.4 mg/d) is $118.35.[34] Patients requiring a tamsulosin dose of 0.8 mg/d incur twice the cost, as 2 tablets are required to achieve this dose.

As expected, the acquisition cost of a month's supply of silodosin is greater than that of a month's supply of the nonselective α_1-blockers available in generic formulations, which include doxazosin (1–8 mg/d: $27.71–$30.54) and terazosin (1–10 mg/d: $43.35–$48.05).[34] The AWP of a 30-day supply of alfuzosin (10 mg/d), a nonselective α_1-blocker that is not available in a generic formulation, is $108.62.[34]

DISCUSSION

Silodosin, the newest member of the α_1-AR antagonists, has higher selectivity for the α_{1A}-AR than for the α_{1B}- and α_{1D}-ARs.[16] The small number of clinical studies conducted in Japan and the United States have found silodosin efficacious in relieving LUTS in men with BPH. In controlled Phase III clinical studies, the reductions in IPSS with silodosin (total daily dose, 8 mg) ranged from 6.3 to 8.3 over 12 weeks, with improvements in symptom scores of 2.9 to 3 points relative to placebo.[11,21,23] This degree of reduction is similar to that typically reported for other α_1-blockers, which have been associated with mean improvements of 2 to 2.5 points in the AUA Symptom Index (AUASI) score compared with placebo.[35] (The IPSS used in the studies reviewed here contains the same 7 questions as the AUASI, with the addition of a separately scored QoL question.) Tamsulosin, in particular, has been associated with a dose-dependent decrease in AUASI score of 1.92 to 3.12 points compared with placebo. The Phase III clinical trial that included both an active-control group (tamsulosin) and a placebo group found a reduction in IPSS of 8.3 points with silodosin, 6.8 points with tamsulosin, and 5.3 points with placebo.[21] Although the investigators concluded that silodosin was noninferior to tamsulosin and superior to placebo, the tamsulosin dose used was 0.2 mg/d. This is the recommended dose in Japan and other Asian countries,[21] but is half that in the United States and is considered suboptimal.[35] Thus, further, comparative studies using appropriate doses are required to confirm the noninferiority of silodosin and tamsulosin in the treatment of BPH-related LUTS.

Silodosin was generally well tolerated in clinical studies. However, it has been associated with a high incidence (>22%) of abnormal or retrograde ejaculation.[11,21,23] Further comparative data are needed to establish the relative incidence of ejaculatory dysfunction with silodosin and tamsulosin. The incidence of vascular effects such as orthostatic hypotension in trials of silodosin was low (<3%); again, comparative data for silodosin and tamsulosin are lacking.

This review was limited by the small number of published studies of silodosin and the short duration of therapy in the available studies.[11,21–23] The longest exposure to silodosin was in the extension study, in which patients who had previously received silodosin for 12 weeks were treated for an additional 40 weeks.[26] Therefore, the long-term efficacy and tolerability of silodosin require further study, particularly given the chronic nature of BPH.

CONCLUSIONS

Silodosin is a selective α_{1A}-AR antagonist that was approved for the treatment of BPH-related LUTS in the United States in 2008. In clinical studies, silodosin was associated with significant improvements in both storage and voiding symptoms, as well as improvements in measures of QoL. Clinical improvements were observed early in the course of treatment and in patients with both moderate and severe symptoms. Before determining whether silodosin's selectivity for the α_{1A}-AR translates into a clinical advantage over other available agents, long-term studies of the comparative efficacy and tolerability of silodosin and other α_1-blockers (particularly tamsulosin) are necessary.

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