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ADIS DRUG EVALUATION

Silodosin: A Review of Its Use in the Treatment of the Signs and Symptoms of Benign Prostatic Hyperplasia

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Abstract Silodosin is a highly selective α_{1A}-adrenoceptor antagonist indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). Oral silodosin had a rapid onset of effect in men with lower urinary tract symptoms (LUTS) associated with BPH, with improvements seen in voiding and storage symptoms, maximum urinary flow rate and health-related quality of life in well-designed, 12-week trials. Silodosin was noninferior to tamsulosin in terms of improving LUTS associated with BPH. The efficacy of silodosin was maintained in 9-month extension studies and was also seen in a phase IV study conducted in a real-world setting. Silodosin was generally well tolerated and was associated with a low risk of orthostatic hypotension. Abnormal ejaculation was the most commonly reported adverse event, although few patients discontinued treatment with silodosin because of this adverse event. In conclusion, silodosin is a useful option for the treatment of LUTS associated with BPH.

Silodosin for treating the signs and symptoms of benign prostatic hyperplasia (BPH): a summary

Highly selective α_{1A}-adrenoceptor antagonist
Rapidly improves lower urinary tract symptoms (LUTS) associated with BPH
Noninferior to tamsulosin in treating LUTS associated with BPH
Efficacy maintained in 9-month extension studies
Generally well tolerated, with a low risk of orthostatic hypotension
Few discontinuations occur because of abnormal ejaculation, which is the most commonly reported adverse event

1 Introduction

The pathophysiology of lower urinary tract symptoms (LUTS) is multifactorial, with benign prostatic hyperplasia (BPH) an important contributing factor [1, 2]. LUTS associated with BPH can have a significant impact on health-related quality of life (HR-QOL) [3]. LUTS are classified as voiding (obstructive) symptoms (e.g. straining, weak stream, hesitancy) [usually attributed to bladder outlet obstruction], storage (irritative) symptoms (e.g. frequency, nocturia, urgency) [usually attributed to increased smooth muscle tone and resistance within the enlarged prostate gland] and postmicturition symptoms (e.g. sensation of incomplete emptying) [1, 4].

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α_{1A}-Adrenoceptors are located in the human prostate, bladder base, bladder neck, prostatic capsule and prostatic urethra and mediate smooth muscle contraction in these tissues [5]. Thus, blocking α_{1A}-adrenoceptors is a rational approach to the treatment of LUTS associated with BPH.

The α_{1A}-adrenoceptor antagonist silodosin (Rapaflo®, Urorec®, Silodyx®, Urief®, Silosin®, Thrupas®) is available in numerous countries for the treatment of the signs and symptoms of BPH. This article reviews the clinical efficacy and tolerability of silodosin in the treatment of LUTS associated with BPH, as well as summarizing its pharmacological properties.

2 Pharmacodynamic Properties

The pharmacodynamic properties of silodosin have been reviewed previously [6]; this section provides a brief overview.

Silodosin is a highly selective α_{1A}-adrenoceptor antagonist [7–9]. Antagonism of α_{1A}-adrenoceptors results in smooth muscle relaxation in the prostate, bladder base, bladder neck, prostatic capsule and prostatic urethra, thereby reducing bladder outlet resistance [10, 11].

Silodosin has low affinity for α_{1B}-adrenoceptors in the cardiovascular system [12]. In vitro, the affinity of silodosin for α_{1A}-adrenoceptors was ≈580-fold greater than for α_{1B}-adrenoceptors and ≈55-fold greater than for α_{1D}-adrenoceptors [9]. By contrast, tamsulosin had ≈15-fold greater affinity for α_{1A}-versus α_{1B}-adrenoceptors and ≈3-fold greater affinity for α_{1A}- versus α_{1D}-adrenoceptors, and prazosin had similar affinity for α_{1A}- and α_{1B}-adrenoceptors and ≈3-fold greater affinity for α_{1D}- versus α_{1A}-adrenoceptors [9].

The affinity of silodosin, tamsulosin and prazosin for human prostate tissue was 214-, 8.3- and 0.3-fold greater, respectively, than for human aorta tissue in receptor binding studies, and 148-, 2.6- and 0.2-fold greater, respectively, than for human mesenteric artery tissue in functional assays [8].

Silodosin improved bladder urodynamic parameters in men with BPH [13, 14]. Silodosin 4 mg twice daily was associated with significant ($p \leq 0.001$) reductions from baseline in detrusor opening pressure [13], detrusor pressure at maximum urinary flow rate (Q_{max}) [13, 14] and the bladder outlet obstruction index [13, 14]. Silodosin recipients had a significant ($p < 0.01$) increase from baseline in the maximum cystometric capacity in one study [13] and in the bladder capacity at first void in a second study [14]. The majority of patients (≥75 %) with detrusor overactivity at baseline experienced resolution or improvement of detrusor overactivity with silodosin therapy [13, 14]. Voiding and storage symptoms and Q_{max} were improved with silodosin in men with LUTS associated with BPH (see Sect. 5 for results of pivotal clinical trials).

In keeping with its selectivity for α_{1A}-adrenoceptors over α_{1B}-adrenoceptors (which help maintain vascular smooth muscle tone), silodosin was associated with a low risk of orthostatic hypotension in men with LUTS associated with BPH (see Sect. 6). In men with BPH who received silodosin 4 or 8 mg/day, positive orthostatic tests occurred in 4.5 and 3.3 % of patients, respectively [15].

In healthy men, therapeutic (8 mg/day) and supratherapeutic (24 mg/day) dosages of silodosin were not associated with prolongation of the heart rate-corrected QT (QTc) interval, according to the results of a thorough QT study [16].

3 Pharmacokinetic Properties

Silodosin had an absolute bioavailability of ≈32 % [11, 17], and demonstrated linear pharmacokinetics over the dosage range of 0.1–48 mg/day [11]. In healthy men who received silodosin 8 mg once daily for 7 days, a mean maximum steady-state plasma concentration (C_{max}) of 61.6 ng/mL was reached (t_{max}) in a mean 2.6 h [17]. At steady state, the mean area under the plasma concentration-time curve (AUC) was 373.4 ng·h/mL [17]. Steady state was reached after administration of silodosin for 3 days [11].

Administering silodosin with food decreased its C_{max} by ≈30 % and increased its t_{max} by ≈1 h [11]; it is recommended that silodosin be administered with food [11, 17]. Administering the contents of a silodosin capsule sprinkled on applesauce was bioequivalent to administering an intact capsule [17].

Silodosin was ≈97 % plasma protein bound with an apparent volume of distribution of 49.5 L [11, 17]. In rats administered radiolabelled silodosin, little radioactivity was detected in the brain, indicating a lack of penetration through the blood-brain barrier [12].

Silodosin was extensively metabolized via glucuronidation, alcohol and aldehyde dehydrogenase, and cytochrome P450 (CYP) 3A4 [11, 17]. Metabolism of silodosin by UDP-glucuronosyltranferase (UGT) 2B7 yielded KMD-3213G, its major glucuronide metabolite, which demonstrated pharmacological activity in vitro [11, 17]. KMD-3213G reached plasma concentrations approximately fourfold higher than those of silodosin, reached steady state in 5 days and had a half-life of ≈24 h [11, 17]. KMD-3293, the secondary major metabolite, is not expected to contribute to the pharmacological activity of silodosin [17].

Approximately 54.9 and 33.5 % of radioactivity was recovered in the faeces and urine, respectively, within 10 days of oral administration of radiolabelled silodosin

[11, 17]. The plasma clearance of silodosin was ≈10 L/h following intravenous administration [17]. Silodosin had a mean elimination half-life of 13.3 h [17].

Unbound silodosin C_{max} and AUC values were on average 1.6- and 1.7-fold higher in patients with mild or moderate renal impairment who received a single dose of the drug than in subjects with normal renal function [11]. In addition, unbound silodosin C_{max} and AUC values were 2.2- and 3.7-fold higher in patients with severe renal impairment who received a single dose of the drug than in subjects with normal renal function [11]. No dosage adjustment is needed in patients with mild renal impairment, although the initial silodosin dosage should be reduced to 4 mg once daily in patients with moderate renal impairment [11, 17]. Silodosin is contraindicated in patients with severe renal impairment in the USA [17] and its use is not recommended in this patient group in the EU [11].

The pharmacokinetics of silodosin were not significantly altered following administration of a single dose to patients with moderate hepatic impairment [11, 17]. No dosage adjustment is needed in patients with mild or moderate hepatic impairment [11, 17]. Silodosin is contraindicated in patients with severe hepatic impairment in the USA [17] and its use in this patient group is not recommended in the EU [11], reflecting the lack of data in severe hepatic impairment [11, 17].

No adjustment of the silodosin dosage is needed in the elderly [11].

Genetic polymorphisms in UGT2B7 (which are relatively common in Asian patients) may affect the pharmacokinetics of silodosin [18]. For example, the silodosin AUC from time zero to infinity was increased by 38 and 25 % in healthy men with UGT2B7*1/*2 and UGT2B7*2/*2, respectively [18].

4 Potential Drug Interactions

Silodosin did not induce or inhibit CYP isozymes in vitro [11, 17].

Silodosin C_{max} and AUC values increased 3.8- and 3.2-fold, respectively, when the strong CYP3A4 inhibitor ketoconazole was coadministered [17]. Coadministration of silodosin and strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir) is contraindicated in the USA [17] and not recommended in the EU [11]. The US prescribing information recommends that caution should be exercised, and adverse events monitored, when silodosin is coadministered with moderate CYP3A4 inhibitors (e.g. diltiazem, erythromycin, verapamil) [17]; the EU summary of product characteristics (SPC) states that no dosage adjustment is required [11].

In vitro data demonstrated that silodosin was a P-glycoprotein (P-gp) substrate, and coadministration of strong P-gp inhibitors (e.g. ciclosporin) and silodosin is not recommended [17]. No significant pharmacokinetic interaction was seen between silodosin and the P-gp substrate digoxin [11, 17].

Silodosin exposure may be increased by the coadministration of UGT2B7 inhibitors (e.g. probenecid, valproic acid, fluconazole) [17].

The US prescribing information states that silodosin should not be used in combination with other α-adrenoceptor antagonists, as pharmacodynamic interactions may occur [17]; the EU SPC does not recommend the coadministration of silodosin and other α-adrenoceptor antagonists [11].

In the silodosin clinical development programme, concomitant antihypertensive therapy with agents that act on the renin-angiotensin system, β-adrenoceptor antagonists, calcium channel antagonists or diuretics was administered to 24, 13, 9 and 8 % of patients, respectively [15]. The risk of orthostatic hypotension did not appear to be increased in patients who received concomitant antihypertensives compared with those who did not [15] (see also Sect. 6). However, the US prescribing information and EU SPC state that caution should be exercised, and patients should be monitored for possible adverse events, when silodosin is coadministered with antihypertensives, as the risk of orthostatic hypotension may be increased [11, 17].

Minimal pharmacodynamic interaction [e.g. orthostatic changes in blood pressure (BP) or heart rate] was seen when silodosin was coadministered with maximum therapeutic doses of the phosphodiesterase (PDE)-5 inhibitors sildenafil and tadalafil [19]. The EU SPC recommends that patients receiving both silodosin and PDE-5 inhibitors be monitored for possible adverse reactions [11] and the US prescribing information recommends caution [17].

5 Therapeutic Efficacy

This section includes trials examining the efficacy of silodosin 8 mg once daily or 4 mg twice daily in patients with LUTS associated with BPH. Approved silodosin dosages are 8 mg once daily in the USA [17] and the EU [11] and 4 mg twice daily in Japan [20] (Sect. 7).

The main focus of this section is the results of randomized, double-blind, parallel-group, multicentre trials [21–25]. Studies were conducted in the USA [21], Europe [22], Japan [23], Taiwan [24] and South Korea [25]. Results of two identically designed US trials are presented as a prespecified pooled analysis [21]. The trials compared silodosin with placebo and/or tamsulosin [21–24] or compared silodosin 8 mg once daily with silodosin 4 mg twice

Table 1 Key inclusion criteria in silodosin trials

Aged ≥40 [24] or ≥50 [21–23, 25, 27] years
IPSS score of ≥8 [23, 25–27] or ≥13 [21, 22, 24]
Q_{max} of <15 mL/s [23–26] or 4–15 mL/s [21, 22]
Voided volume of ≥100 mL [23, 24] or ≥125 mL [22]
Residual urine volume of <100 mL [23], <200 mL [25] or <250 mL [21]
Prostate volume ≥20 mL [23–26]
IPSS QOL score of ≥3 [23–27]

IPSS International Prostate Symptom Score, *QOL* quality of life, Q_{max} maximum urinary flow rate

daily [25]. Key inclusion criteria are shown in Table 1. The primary endpoint was the mean change from baseline to week 12 in the total International Prostate Symptom Score (IPSS) [21–25].

Two additional randomized, multicentre, Japanese studies comparing silodosin with naftopidil are also briefly discussed in this section [26, 27]; one study was of open-label design [26] and blinding was not specified in the other study [27]. Key inclusion criteria are shown in Table 1.

Results of a European phase IV study, which examined the use of silodosin in a real-world setting and is available as a poster, are also briefly discussed [28].

5.1 Comparisons with Placebo

Silodosin was effective in the treatment of LUTS associated with BPH. Significantly greater reductions from baseline to week 12 in the total IPSS score were seen with silodosin 8 mg once daily [21, 22] or 4 mg twice daily [23] than with placebo (Table 2). Recipients of silodosin 8 mg once daily [21, 22] or 4 mg twice daily [23] also had significantly greater reductions from baseline to week 12 in IPSS voiding and storage symptom scores (Table 2).

Rapid improvement in symptoms was seen with silodosin, with significant ($p < 0.0005$ vs. placebo) improvements in the total IPSS score and IPSS voiding and storage symptom scores seen 3–4 days after starting treatment in the US studies [21]. Post hoc analysis of the US studies demonstrated that each IPSS symptom (i.e. frequency, urgency, nocturia, incomplete emptying, intermittency, weak stream, straining) improved from baseline to week 12 to a significantly ($p < 0.01$) greater extent with silodosin than with placebo [29].

At study end, a decrease in the IPSS total score of ≥25 % (i.e. IPSS response) was seen in significantly more silodosin 4 mg twice daily than placebo recipients in the Japanese study (76.4 vs. 50.6 %; $p < 0.001$) [23] and in significantly more silodosin 8 mg once daily than placebo recipients in a post hoc, pooled analysis of the US and European studies (59.3 vs. 37.4 %; $p < 0.001$) [30].

At week 12, Q_{max} was significantly increased from baseline with silodosin 8 mg once daily in the US studies [21], but not in the European study [22] (Table 2). Q_{max} had increased to a significantly ($p < 0.0001$) greater extent with silodosin than with placebo within 2–6 h in the US studies [21]. In a post hoc analysis of the Japanese study in patients with an increase from baseline in voided volume of <50 %, the increase in Q_{max} was significantly greater with silodosin 4 mg twice daily than with placebo [23] (Table 2).

A post hoc, pooled analysis of the US and European studies found that significantly more silodosin than placebo recipients reported an improvement in nocturia (53.4 vs. 42.8 %; $p < 0.0001$) and significantly fewer silodosin than placebo recipients reported worsening of nocturia (9.0 vs. 14.3 %; $p < 0.0001$) by study end [31]. Among patients with at least two nocturnal voiding episodes at baseline, significantly more silodosin than placebo recipients had less than two nocturnal voiding episodes at study end (29.3 vs. 19.0 %; $p = 0.0002$) [31].

In a post hoc analysis of the European study, significantly more silodosin than placebo recipients had a reduction from baseline in nocturia of at least one episode (59 vs. 45 %; $p = 0.01$), with no significant difference seen between tamsulosin and placebo recipients (54 vs. 45 %) [32]. Similarly, among the subgroup of patients with at least two episodes of nocturia at baseline, significantly more silodosin than placebo recipients had a reduction from baseline in nocturia of at least one episode (67 vs. 55 %; $p < 0.05$), with no significant difference seen between tamsulosin and placebo recipients (63 vs. 55 %). In addition, significantly ($p < 0.05$) more silodosin than placebo recipients had a simultaneous improvement in the bothersome symptoms of incomplete emptying, frequency and nocturia, both in the overall population (35 vs. 25 %) and in the subgroup of patients with at least two episodes of nocturia at baseline (40.7 vs. 30.6 %) [32].

Another post hoc, pooled subgroup analysis of the US and European studies revealed that silodosin was significantly ($p < 0.05$) more effective than placebo regardless of patient age (≤65 years or >65 years), baseline IPSS score (<20 or ≥20), baseline Q_{max} (≤10 or >10 mL/s), baseline prostate specific antigen (PSA) level (≤1.5 or >1.5 ng/mL), concomitant use of antihypertensive agents or baseline renal function (normal or impaired renal function) in terms of improving IPSS-related parameters (i.e. total IPSS score, IPSS voiding and storage symptom scores, IPSS QOL scores and IPSS response rate) [33]. Q_{max} also improved to a significantly ($p \leq 0.05$) greater extent with silodosin than with placebo in most of these patient subgroups, although no significant difference was seen between silodosin and placebo in patients with a baseline IPSS score of <20, Q_{max} of >10 mL/s or PSA level of ≤1.5 ng/mL [33].

Table 2 Efficacy of silodosin in the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia

Study (Country/region)	Treatment (mg)	No. of pts[a]	Mean change from baseline to week 12 (mean baseline value)			
			Total IPSS score[b]	IPSS voiding symptoms score	IPSS storage symptoms score	Q_{max} [mL/s]
Comparisons with PL and/or TAM						
Marks et al. [21][c,d] (USA)	SIL 8 od	466	−6.4*** (21.3)	−4.0*** (12.0)	−2.3*** (9.3)	2.6** (8.7)
	PL	457	−3.5 (21.3)	−2.1 (12.0)	−1.4 (9.3)	1.5 (8.9)
Chapple et al. [22][d] (Europe)	SIL 8 od	371	−7.0**[,e] (19)	−4.5** (11)	−2.5* (8)	3.77 (11)
	TAM 0.4 od	376	−6.7** (19)	−4.2** (11)	−2.4* (8)	3.53 (10)
	PL	185	−4.7 (19)	−2.9 (11)	−1.8 (8)	2.93 (10)
Kawabe et al. [23] (Japan)	SIL 4 bid	175	−8.3**[,e] (17.1)	−5.8**[,†] (10.8)	−2.5* (6.4)	1.70*[,f] (9.9)
	TAM 0.2 od	192	−6.8 (17.0)	−4.8 (10.8)	−2.1 (6.2)	2.60[f] (9.4)
	PL	89	−5.3 (17.1)	−3.8 (10.9)	−1.5 (6.3)	0.26[f] (10.2)
Yu et al. [24] (Taiwan)	SIL 4 bid	87	−10.6[e] (19.3)	−7.1 (12.1)	−3.5 (7.1)	0.9 (10.3)
	TAM 0.2 od	83	−10.0 (19.8)	−6.7 (13.0)	−3.3 (6.9)	1.6 (10.6)
SIL 8 mg od vs. 4 mg bid						
Choo et al. [25] (South Korea)	SIL 8 od	205	−6.7[g] (18.6)	−4.4 (11.8)	−2.1 (6.9)	3.55 (10.6)
	SIL 4 bid	202	−6.9 (19.4)	−4.7 (11.9)	−2.5 (7.5)	3.74 (10.3)

Results of randomized, double-blind, parallel-group, multicentre trials of 12 weeks' duration

bid twice daily, *IPSS* International Prostate Symptom Score, *ITT* intent-to-treat, *od* once daily, *PL* placebo, *pts* patients, Q_{max} maximum urinary flow rate, *SIL* silodosin, *TAM* tamsulosin

* $p < 0.01$, ** $p < 0.001$, *** $p < 0.0001$ vs. PL; † $p < 0.05$ vs. TAM

[a] No. of pts in the ITT [21], modified ITT [22, 25] or per-protocol [24] population or the full analysis set [23]

[b] Primary endpoint. The total IPSS score is the sum of seven questions rated on a 6-point scale that assess storage (frequency, urgency, nocturia) and voiding (incomplete emptying, intermittency, weak stream, straining) symptoms

[c] Pooled analysis of two trials

[d] Trials included a 4-week PL run-in period. Pts with a ≥25 % [22] or ≥30 % [21] reduction in IPSS score or an increase in Q_{max} score of ≥3 mL/s [21] during the run-in period were excluded from randomization. Pts also had to have 80–120 % compliance during the run-in period [22]

[e] SIL was noninferior to TAM

[f] Subgroup analysis in pts with a change from baseline in voided volume of <50 %

[g] SIL 8 od was noninferior to SIL 4 bid

In terms of HR-QOL, the proportion of patients delighted, pleased or mostly satisfied with their urinary condition at baseline versus week 12 was 6.9 versus 32.0 % with silodosin and 7.2 versus 22.5 % with placebo in the US studies [21] and 7.8 versus 44.0 % with silodosin and 6.5 versus 34.0 % with placebo in the European study [22]. In the Japanese study, the IPSS QOL score improved to a significantly ($p = 0.002$) greater extent with silodosin than with placebo [23].

The efficacy of silodosin was maintained in the longer term, according to the results of 9-month open-label extensions of the US [34] and European [35] studies. In the US extension phase, all patients originally randomized to silodosin or placebo received silodosin 8 mg once daily for 40 weeks [34]. At the start of the extension phase, patients originally randomized to silodosin ($n = 314$) had a mean IPSS total score of 14.5 which had decreased by 1.6 points at week 40, and patients originally randomized to placebo ($n = 347$) had a mean IPSS total score of 17.8 which had decreased by 4.5 points at week 40 in the observed cases analysis [34]. In the European extension phase (available as an abstract), all patients originally randomized to silodosin, tamsulosin or placebo received silodosin 8 mg once daily for 40 weeks [35]. At the end of the extension phase, the mean IPSS total score had decreased by 1.0, 0.6 and 3.0 points in patients originally randomized to silodosin, tamsulosin or placebo, respectively [35].

5.2 Comparisons with Tamsulosin

Silodosin 8 mg once daily was noninferior to tamsulosin 0.4 mg once daily [22] and silodosin 4 mg twice daily was noninferior to tamsulosin 0.2 mg once daily [23, 24] in terms of the reduction from baseline to week 12 in the total IPSS score (Table 2). In the European study, the mean change from baseline in the total IPSS score was 0.3 units (intent-to-treat analysis) or 0.4 units (per-protocol analysis) in favour of silodosin, although the difference between silodosin and tamsulosin was not statistically significant [22].

In terms of the proportion of patients with a reduction in the IPSS score of ≥25 %, there was no significant difference between silodosin and tamsulosin recipients in the European (66.8 vs. 65.4 %) [22] or Taiwanese (86.2 vs. 81.9 %) [24] studies, although significantly more silodosin than tamsulosin recipients achieved this endpoint in the Japanese study (76.4 vs. 65.6 %; $p = 0.028$) [23].

In general, reductions from baseline to week 12 in IPSS voiding and storage symptom scores did not significantly differ between silodosin and tamsulosin recipients [22–24], although in the Japanese study, a significantly greater reduction from baseline in the IPSS voiding symptom score was seen with silodosin than with tamsulosin [23] (Table 2).

Where specified, the improvement from baseline in Q_{max} did not significantly differ between silodosin and tamsulosin recipients in the Taiwanese study [24] or in a post hoc analysis in patients with an increase from baseline in voided volume of <50 % in the Japanese study [23] (Table 2).

In a post hoc analysis of the European study, significantly ($p = 0.03$) more silodosin than tamsulosin recipients had a simultaneous improvement in the bothersome symptoms of incomplete emptying, frequency and nocturia, both in the overall population (35 vs. 27.7 %) and in the subgroup of patients with at least two episodes of nocturia at baseline (40.7 vs. 32.4 %) [32].

The proportion of patients delighted, pleased or mostly satisfied with their urinary condition at baseline versus week 12 was 7.8 versus 44.0 % with silodosin and 8.5 versus 44.7 % with tamsulosin in the European study [22]. The change from baseline in the IPSS QOL score did not significantly differ between silodosin and tamsulosin recipients in the other two studies [23, 24].

5.3 Silodosin 8 mg Once Daily Versus 4 mg Twice Daily

Silodosin 8 mg once daily was noninferior to silodosin 4 mg twice daily in terms of the reduction from baseline to week 12 in the total IPSS score (Table 2) [25]. Moreover, there were no significant differences between silodosin 8 mg once daily recipients and silodosin 4 mg twice daily recipients in the change from baseline to week 12 in IPSS voiding and storage symptom scores or Q_{max} (Table 2) [25].

The proportion of patients with a ≥25 % reduction in the total IPSS score (63 vs. 68 %), a ≥4-point reduction in the total IPSS score (66 vs. 69 %) or a ≥30 % improvement in Q_{max} (47 vs. 41 %) did not significantly differ between silodosin 8 mg once daily and silodosin 4 mg twice daily recipients [25].

The change from baseline in the IPSS QOL score did not significantly differ between patients receiving silodosin 8 mg once daily and those receiving silodosin 4 mg twice daily [25].

5.4 Additional Trials

5.4.1 Comparisons with Naftopidil

The open-label trial included α_{1A}-adrenoceptor antagonist-naïve patients ($n = 68$) or patients who had received tamsulosin for ≥3 months and wanted to switch to another oral drug ($n = 53$) [26]. Patients received silodosin 4 mg twice daily or naftopidil 50 mg once daily for 8 weeks. Among α_1-adrenoceptor antagonist-naïve patients (34 silodosin and 32 naftopidil recipients), the mean total IPSS score was reduced to a significantly greater extent with silodosin than with naftopidil at week 8 (−7.2 vs. −2.7; $p = 0.004$). The mean IPSS storage symptom score (−2.6 vs. −0.9; $p = 0.007$), but not the IPSS voiding symptom score (−3.5 vs. −1.4), also decreased to a significantly greater extent with silodosin than with naftopidil. The mean increase in Q_{max} did not significantly differ between silodosin and naftopidil recipients (0.9 vs. 0.8 mL/s). Among tamsulosin-experienced patients (22 silodosin and 24 naftopidil recipients), mean improvements from baseline in the total IPSS score (−4.2 vs. −4.7), the IPSS voiding symptom score (−2.1 vs. −2.3), the IPSS storage symptom score (−1.4 vs. −1.8) and Q_{max} (1.5 vs. 1.3 mL/s) did not significantly differ between silodosin and naftopidil recipients [26].

In the other trial, patients received silodosin 8 mg/day ($n = 53$) or naftopidil 75 mg/day ($n = 44$) for 12 weeks [27]. Mean changes from baseline in the total IPSS score (−7.1 vs. −5.7), the IPSS storage symptom score and Q_{max} (1.9 vs. 3.6 mL/s) did not significantly differ between silodosin and naftopidil recipients. However, the IPSS voiding symptom score decreased to a significantly ($p = 0.014$) greater extent with silodosin than with naftopidil [27].

5.4.2 European Phase IV Study

The noncomparative, multinational, European, phase IV study included 1,036 men with LUTS associated with BPH (IPSS score of ≥12) who received silodosin 8 mg once daily for 24 weeks [28].

At study end, the mean IPSS total score, IPSS voiding and storage symptom scores and IPSS QOL score had decreased by 8.3, 5.1, 3.2 and 1.8, respectively, with silodosin (mean baseline scores of 18.9, 10.8, 8.1 and 4.0, respectively) [28]. A reduction in the IPSS total score of ≥25 % was seen in 77.1 % of silodosin recipients, with a decrease of >3 points seen in 80.8 % [28].

Of the symptoms reported as most bothersome/frequent at baseline (i.e. nocturia, frequency, decreased stream, urgency, terminal dribbling, incomplete emptying) [as assessed using the International Continence Society-male questionnaire], improvements in bother were reported in 43.8–54.7 % of silodosin recipients and improvements in frequency were reported in 47.5–56.9 % of silodosin recipients [28].

6 Tolerability

Oral silodosin was generally well tolerated in the treatment of men with LUTS associated with BPH [21–25], with the majority of reported adverse events being of mild severity [24].

In a pooled analysis [30] of the US [21] and European [22] trials, adverse drug reactions were reported in significantly more silodosin than placebo recipients (29.0 vs. 7.3 %; $p < 0.001$), and significantly more silodosin than placebo recipients discontinued the study because of treatment-emergent adverse events (4.3 vs. 1.7 %; $p < 0.001$).

Abnormal ejaculation was the most common adverse event reported by silodosin recipients in clinical studies [21–25]. For example, the incidence of retrograde ejaculation was significantly higher with silodosin than with placebo in the pooled analysis of the US and European trials (22.0 vs. 0.9 %; $p < 0.001$) [30]. The incidence of abnormal/retrograde ejaculation was also significantly higher (9.7 vs. 1.0 %; $p = 0.009$ [24] and 14.2 vs. 2.1 %; $p < 0.05$ [22]) or numerically higher (22.3 vs. 1.6 % [23]) in silodosin than in tamsulosin recipients. In the phase IV study conducted in a real-world setting, ejaculation failure was reported in 17.9 % of silodosin recipients [28]. However, only 1.3–2.9 % of silodosin recipients discontinued treatment because of abnormal ejaculation in these studies [22–24, 28]. Ejaculation failure was reversible following discontinuation of silodosin [22]. Post hoc analyses [36, 37] of the US [21] and Japanese [23] studies suggested that abnormal ejaculation may be associated with greater improvements in LUTS. For example, in the US studies, silodosin recipients with retrograde ejaculation were significantly ($p = 0.0127$) more likely than silodosin recipients without retrograde ejaculation to experience both an improvement of ≥3 points in the IPSS total score and an improvement of ≥3 mL/s in Q_{max} [36].

In the pooled analysis of the US and European trials, the incidence of dizziness (1.9 vs. 0.6 %; $p = 0.029$) and nasal congestion (0.9 vs. 0.2 %; $p = 0.027$) was also significantly higher with silodosin than with placebo, although there was no significant difference between silodosin and placebo recipients in the incidence of other adverse drug reactions, including erectile dysfunction (0.7 vs. 0.3 %) and loss of libido (0.5 vs. 0.2 %) [30].

The tolerability profile of silodosin did not appear to differ between patients receiving the 8 mg once daily dosage and those receiving the 4 mg twice daily dosage [25].

The incidence of orthostatic hypotension was generally low in silodosin recipients [28, 30]. For example, the incidence of orthostatic hypotension was 1.3 % in silodosin recipients and 1.1 % in placebo recipients in the pooled analysis of the US and European trials [30]. Approximately 30 % of patients in these trials were receiving concomitant antihypertensive medication; the risk of orthostatic hypotension did not significantly differ between silodosin and placebo recipients among patients receiving concomitant antihypertensives (1.8 vs. 2.0 %) or among patients not receiving concomitant antihypertensives (1.1 vs. 0.7 %) [33]. It should be noted that pivotal trials generally excluded patients with a history of orthostatic hypotension [23, 25], significant orthostatic hypotension [21, 22] or severe hypotension [24]. Hypotension was reported in 0.7 % of silodosin recipients in the phase IV study; 60.5 % of patients in this study had concomitant cardiovascular disease [28].

Intraoperative floppy iris syndrome has been reported in some patients undergoing cataract surgery who are receiving or have previously received α_1-adrenoceptor antagonists [11, 17], including patients who had been treated with silodosin [17, 38]. Ophthalmologists should be informed about the use of α_1-adrenoceptor antagonists prior to patients undergoing cataract surgery [1].

No clinically significant changes in laboratory parameters, ECG recordings or vital signs were reported in silodosin recipients in the European trial [22]. In particular, changes in supine systolic BP, diastolic BP and heart rate did not significantly differ between silodosin and placebo recipients [22]. No clinically significant differences were seen between silodosin and tamsulosin recipients in terms of systolic BP, diastolic BP or heart rate in the Japanese study [23] or in terms of standing systolic or diastolic BP or sitting diastolic BP in the Taiwanese study [24], although a significantly ($p = 0.02$) greater reduction in sitting systolic BP was seen with tamsulosin than with silodosin [24].

The tolerability profile of silodosin in the 9-month extensions of the US [34] and European [35] studies was consistent with that seen in 12-week studies. For example, in the US extension, adverse events were reported in 65.2 % of patients, with drug-related adverse events reported in 28.4 % [34]. Mild, moderate and severe adverse events were reported in 50.7, 29.0 and 5.4 % of patients, respectively. No serious adverse events that were considered drug related were reported during the extension phase.

The most commonly reported adverse events included retrograde ejaculation (20.9 % of patients), diarrhoea (4.1 %), nasopharyngitis (3.6 %), dizziness (2.9 %), upper respiratory tract infection (2.7 %), arthralgia (2.6 %), orthostatic hypotension (2.6 %), increased PSA levels (2.1 %) and nasal congestion (2.0 %). Among patients originally randomized to placebo and silodosin, retrograde ejaculation was reported in 31.1 and 9.6 %, respectively, with discontinuation because of retrograde ejaculation occurring in 7.5 and 1.9 %. No drug-related cardiac disorders or prolongation of the QTc interval was reported [34].

7 Dosage and Administration

Silodosin is approved in the USA [17] and the EU [11] for the treatment of the signs and symptoms of BPH, and in Japan for the treatment of bladder outlet obstruction associated with BPH [20]. The recommended silodosin dosage is 8 mg once daily in the USA [17] and the EU [11] and 4 mg twice daily in Japan [20].

Local prescribing information should be consulted for more information regarding contraindications, warnings and precautions associated with silodosin.

8 Place of Silodosin in the Management of Benign Prostatic Hyperplasia

The key goals in the treatment of LUTS associated with BPH are to alleviate bothersome symptoms and improve HR-QOL [3]. Guidelines from the European Association of Urology (EAU) [1] and American Urological Association [3] recommend α_1-adrenoceptor antagonists for the first-line treatment of LUTS associated with BPH. The more recent EAU guidelines include silodosin as a treatment option [1]. Other α_1-adrenoceptor antagonists include alfuzosin, doxazosin, tamsulosin and terazosin, with the α_{1D}-adrenoceptor-selective antagonist naftopidil also available in some countries, including Japan [1, 2].

α_1-Adrenoceptor antagonists are the most commonly prescribed agents for LUTS associated with BPH [39]. Given that the efficacy of the various α_1-adrenoceptor antagonists is generally considered similar [40], factors that may influence treatment choice include speed of onset, tolerability (e.g. propensity for cardiovascular adverse events), convenience, cost and patient preference [41]. In a retrospective study in Korean men with LUTS associated with BPH, patients receiving silodosin were significantly ($p < 0.05$) less likely to have a prescription change than those receiving tamsulosin, doxazosin or alfuzosin (16.3 vs. 20.2, 25.8 and 25.5 % of patients) [41].

Silodosin had a rapid onset of effect and was effective in the treatment of LUTS associated with BPH, according to the results of pivotal clinical trials (Sect. 5). Efficacy was maintained in 9-month extension studies and was also seen in a phase IV study conducted in a real-world setting; longer-term efficacy data would be of interest.

Silodosin was noninferior to tamsulosin in the treatment of LUTS associated with BPH (Sect. 5.2). The Japanese and Taiwanese studies compared silodosin 4 mg twice daily with tamsulosin 0.2 mg once daily, which is the approved tamsulosin dosage in Japan and some other Asian countries, although some consider this dosage suboptimal [42]; the approved tamsulosin dosage in the USA [43] and the EU [44] is 0.4 mg once daily. Results of two small trials also indicate that silodosin was at least as effective as naftopidil in the treatment of LUTS associated with BPH (Sect. 5.4.1).

Oral silodosin was generally well tolerated, including in 9-month extension studies (Sect. 6). Abnormal ejaculation was the most commonly reported adverse event, reflecting the selective antagonism of α_{1A}-adrenoceptors by silodosin. However, few patients discontinued treatment with silodosin because of abnormal ejaculation. Younger, sexually active men may consider abnormal ejaculation to be more of an issue than older patients [5, 45].

Given that patients with LUTS associated with BPH are usually older and often have comorbidities requiring medication, avoiding cardiovascular events is an important consideration in this patient group [46]. Orthostatic hypotension is commonly associated with nonselective α_1-adrenoceptor antagonists such as doxazosin and terazosin [46]. However, silodosin was associated with a low risk of orthostatic hypotension in clinical trials and a low risk of hypotension in a phase IV trial conducted in the real-world setting in which the majority of patients had cardiovascular comorbidities (Sect. 6). Moreover, the coadministration of antihypertensive drugs did not appear to increase the risk of orthostatic hypotension in silodosin recipients (Sects. 4, 6). This suggests a role for silodosin in the treatment of patients at particular risk for orthostatic hypotension because of cardiovascular comorbidities or concomitant antihypertensive therapy [45, 47, 48].

The low risk of orthostatic hypotension associated with silodosin presumably reflects its high selectivity for α_{1A}-adrenoceptors over α_{1B}-adrenoceptors (Sect. 2). Tamsulosin, which has moderate selectivity for α_{1A}-adrenoceptors over α_{1B}-adrenoceptors [12, 49], appears to be associated with an increased risk of severe hypotension during the first 8 weeks of treatment ('first-dose phenomenon') [50]. It is recommended that tamsulosin be administered after the same meal each day [43, 44], as administration in the fasted state may be associated with increased exposure and an increased risk of BP lowering [51]. The timing of silodosin

administration is less restrictive, although it is recommended that silodosin be administered with food [11, 17] (and preferably at the same time each day [11]) in order to reduce the risk of adverse events [17].

In terms of adherence to treatment, some patients prefer α_1-adrenoceptor antagonists that are administered once daily over agents that are administered twice daily [52]. Silodosin is recommended for once-daily use in some countries (e.g. the USA and the EU) and for twice-daily use in others (e.g. Japan) (Sect. 7). A recent well-designed trial demonstrated no differences in efficacy or tolerability between once-daily and twice-daily administration of silodosin (Sects. 5.3, 6).

Silodosin also demonstrated efficacy in acute urinary retention associated with BPH [53], as well as in conditions other than BPH, including chronic prostatitis/chronic pelvic pain syndrome [54], LUTS following prostate cancer brachytherapy [55, 56] and ureteral stones [57, 58], although more data are needed.

In conclusion, silodosin is a useful option for the treatment of LUTS associated with BPH.

Data selection sources: Relevant medical literature (including published and unpublished data) on silodosin was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 15 December 2014], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Silodosin, KM-3213, KSO-0400, Rapaflo, Silodyx, Thrupas, Urief, benign prostatic hyperplasia, BPH.
Study selection: Studies in patients with benign prostatic hyperplasia who received silodosin. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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