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New Drug Review: Silodosin (Rapaflo®)

Indications

Silodosin is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).[1] BPH without obstruction is not a covered Oregon Health Plan (OHP) diagnosis. There are no off-label indications. Silodosin is not to be used in the treatment of hypertension.[1]

Background

Silodosin is a selective alpha-1 adrenergic receptor antagonist used in the management of BPH. Studies have shown that alpha-1 adrenergic receptor antagonists help to reduce symptoms and prevent clinical progression of BPH.[2]

Alpha-1 adrenoreceptors are located in the prostate, bladder base, bladder neck, prostatic capsule and prostatic urethra. Silodosin and tamsulosin (Flomax®) are selective antagonists at the alpha-1a receptors and proposed to cause less risk of hypotension compared to older non-selective agents that inhibit alpha-1b and alpha-1d adrenoreceptors, which help maintain vascular smooth muscle tone.[1,3]

BPH is evaluated using the International Prostate Symptom Score (IPSS). Mild BPH is defined as IPSS scores ≤ 7 and moderate to severe BPH is ≥ 8. A clinically significant change is noted by patients when IPSS scores are reduced by 4 or more.[4]

The American Urological Association guidelines recommend the use of alpha-adrenergic blocker therapy for patients with lower urinary tract symptoms (LUTS) secondary to BPH. The alpha-1 blockers alfuzosin, doxaszosin, tamsulosin and terazosin were evaluated and determined by the guideline panel to have equal clinical effectiveness, although adverse-event profiles differ slightly. Guideline recommendations were made before the development of silodosin; however, studies have shown silodosin and tamsulosin, both selective alpha-1a adrenergic receptor antagonists, to have similar efficacy and adverse effect profiles.[4,5]

Clinical Pharmacology

Silodosin is an alpha-1 adrenergic receptor antagonist, with high affinity for the apha-1A subtype. This type of receptor blockage causes relaxation of smooth muscle in the prostate, bladder base, bladder neck, prostatic capsule, and prostatic urethra resulting in improved urine flow and improvement in BPH symptoms.

Clinical Efficacy

The clinical efficacy of Silodosin was evaluated in a randomized, double blind, placebo controlled trial in 457 patients. Eligible patients were ≥50 years, had an IPSS of ≥8, a quality-of-life (QoL) score ≥3 and a maximum urinary flow rate (Qmax) of <15mL/s. Patients were randomized to silodosin 4mg twice daily, tamsulosin 0.2mg daily or placebo for 12 weeks.[6]

The primary objective of the study was the change in IPSS from baseline. Silodosin statistically significantly decreased IPSS compared to placebo from week 1 and continued through week 12. Total change in IPSS scores from baseline were -8.3 for silodosin, -6.8 for tamsulosin, and -5.3 for placebo. Adverse events incidence rates were 88.6%, 82.3% and 71.6% for silodosin, tamsulosin

and placebo, respectively. Adverse event rates resulting in study withdrawal were 10.2% for silodosin, 5.7% for tamsulosin and 4.5% for placebo. The most common adverse event for silodosin was abnormal ejaculation, 22.3% for silodosin compared to 1.6% for tamsulosin. This accounted for 2.9% of patients discontinuing silodosin therapy for this reason.[6]

Additional studies were done to evaluate the safety and efficacy of silodosin in two randomized, placebo controlled, phase 2 and phase 3 studies. Eligible participants were men 50 years or older with an IPSS score of ≥13. Patients were randomized to 8mg silodosin or placebo with breakfast for 12 weeks.[5]

The primary endpoint was the change in IPSS score from baseline to last observation. IPSS scores for patients taking silodosin were superior to placebo, -6.4 vs. placebo -3.5 ($p < 0.0001$). Patients receiving silodosin discontinued treatment due to adverse events more often than patients receiving placebo, 6.4% and 2.2%, respectively. Orthostatic hypotension was observed in 2.6% of silodosin patients and 1.5% of placebo patients.[5]

Drug Safety and Adverse Effects

The most common adverse reactions (frequency ≥2%) experienced with silodosin are retrograde ejaculation, dizziness, diarrhea, orthostatic hypotension, headache, nasopharyngitis, and nasal congestion. Studies show that silodosin may cause slightly less orthostatic hypotension than tamsulosin.[5,7] It is recommended that silodosin be taken with food to reduce adverse events.[1]

Postural hypotension may occur when starting silodosin. Patients should be cautioned about driving, operating machinery, or partaking in other hazardous tasks. A study in geriatric patients (≥65 years) found orthostatic hypotension in 2.9% of patients (1.9% for placebo) compared with 2.3% of patients <65 years of age (1.2% for placebo).[1]

Intraoperative floppy iris syndrome has been observed in patients undergoing cataract surgery. Patients should notify their ophthalmologist that they are taking silodosin.[1]

Silodosin is contraindicated in patients with severe renal impairment (CCr <30 ml/min) and severe hepatic impairment (Child-Pugh score ≥10). The dose of silodosin should be reduced to 4mg daily in patients with moderate renal impairment (CCr 30-50 ml/min). Silodosin should not been given concomitantly with strong cytochrome P450 3A4 inhibitors (e.g., itraconazole, clarithromycin, ritonovir). In vitro studies indicate that silodosin is a p-glycoprotein (P-gp) substrate, therefore, it is recommended that silodosin not be taken with strong P-gp inhibitors (e.g., cyclosporine) Use of silodosin with other alpha-blockers is not recommended. Silodosin is not indicated for use in females.[1]

Unanswered Safety Concerns: Studies in patients with co-morbidities is needed.

Summary and Recommendations

- Studies have shown the efficacy and adverse events associated with silodosin are consistent with that of other alpha-1 adrenergic antagonists.
- It is recommended that silodosin require a prior authorization for OHP coverage and be added to the existing PA criteria.

References

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