drug information perspectives

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Contents

Tamsulosin
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TAMSULOSIN

SYNONYM: Amsulosin

TRADE NAME: Flomax

CLASSIFICATION: Alpha-1 adrenergic blocker (third generation, uroselective)

ACTION: Selectively blocks alpha-1A adrenergic receptors, which predominate in the prostate, bladder neck and urethra, and alpha-1D adrenergic receptors found in the prostate. Minimal affinity for alpha-1B adrenergic receptors, found in vascular smooth muscle. Enhances bladder emptying by inhibiting smooth muscle contraction in the prostate and bladder neck, which produces improvement in dynamic voiding symptoms and maximum urinary flow rate. Blockade of alpha-1A and alpha-1D adrenergic receptors in the bladder, and possibly blockade of alpha adrenergic receptors in the sympathetic nervous system and spinal cord, produce inhibition of detrusor muscle contractions, and reduction of detrusor muscle instability and storage symptoms.

PHARMACOKINETICS
- **Half-life**: 9-13 hours in healthy volunteers.
- **Absorption**: Absorption is gradual, with bioavailability of close to 100% under fasting conditions. When given with food, the rate and extent of absorption is decreased, and the time to peak plasma level is increased. Peak plasma levels occur about 4 to 8 hours post-dose.
- **Distribution**: Highly protein bound (approximately 99%), predominantly to alpha-1 acid glycoprotein; small volume of distribution (approximately 0.2 L/kg).
- **Metabolism**: Metabolized in the liver, with negligible first-pass metabolism, primarily by cytochrome P450 enzymes 2D6 and 3A4; several glucuronide and sulfate metabolites identified which are not significantly active. Exhibits linear kinetics.
- **Elimination**: Water-soluble metabolites are renally excreted; 8.7-14% excreted as unchanged drug. In healthy volunteers receiving a 0.2 mg oral dose, 76.4% eliminated in the urine, and 21.4% in the feces.

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- **Special Populations**:
    - **Patients with impaired hepatic function**: No significant alteration in pharmacokinetics with mild to moderate impairment; no data in patients with severe dysfunction. Although protein binding is altered, the active unbound concentration and clearance are not significantly affected.
    - **Patients with impaired renal function**: Although AUC is increased, concentration of active unbound drug is not affected. No significant alteration in pharmacokinetic properties; no data in patients with CrCl < 10mL/min.
    - **Elderly**: Half-life increased to 14-15 hours.

USES AND EFFICACY

Uses: Symptomatic treatment of **benign prostatic hyperplasia (BPH);** increases urine flow rates, and decreases residual urine volume and symptom scores. Used to treat voiding symptoms including hesitancy, intermittency, weak stream, the sensation of incomplete emptying of the bladder, terminal urine dribbling, abdominal straining, and storage symptoms such as frequency, urgency, and nocturia.

Major clinical trials

A randomized, double-blind, placebo-controlled trial evaluated the effect of tamsulosin 0.4 mg daily for 12 weeks, following a 2-week placebo run-in period, in 296 patients with symptomatic BPH of mild to moderate severity and a modest impairment of urinary flow rate. Improvement in maximum urinary flow rate was a mean of 1.4 mL/sec (13.1%) in the tamsulosin group vs a mean of 0.4 mL/sec (3.8%) in the placebo group. The mean reduction in the total symptom score was reported as 35.8% and 23.7% in the tamsulosin and placebo groups, respectively. An improvement of symptom score of greater than or equal to 25% has been proposed to be clinically significant for the symptom score scale utilized in this study; after 12 weeks of therapy, 67% of tamsulosin-treated patients and 44% of placebo-treated patients had a 25% or greater decrease in total symptom score. The differences between the results of the tamsulosin and placebo treatment groups regarding urinary flow rate, irritative and obstructive symptom scores, and symptoms of nocturia and hesitancy were statistically significant.

The effectiveness of tamsulosin 0.4 mg or 0.8mg daily for 13 weeks, in patients with moderate to severe signs and symptoms of BPH (n=735) was evaluated in a randomized, double-blind, placebo-controlled trial. Tamsulosin 0.4 mg daily, 0.8 mg daily or placebo produced a 25% or greater reduction in symptom scores in 56, 55 and 40% of patients, respectively, and a 30% or greater increase in urine peak flow rate in 33, 34 and 24% of patients, respectively. The differences between the results in the tamsulosin groups and the placebo treatment group were statistically significant.

A randomized, double-blind, placebo-controlled trial (n=756) assessed the efficacy of tamsulosin 0.4 mg or 0.8 mg daily for 13 weeks (patients randomized to receive tamsulosin 0.8 mg daily received 0.4 mg daily during the first week of treatment); in an extension of this study to assess long-term efficacy and safety of tamsulosin, 418 patients continued to receive the same double-blind medication at the same dose, for a further 40 weeks. Therapy with placebo, tamsulosin 0.4 mg daily, or tamsulosin 0.8 mg daily produced the following results, respectively: (1) a mean percentage reduction in the total symptom score of 28, 42 and 48%, (2) a 25% or greater reduction in symptom scores in 51, 70, and 74% of patients, (3) a mean percentage increase in peak urine flow of 5.3, 18.5 and 18.6%, and (4) a 30% or greater increase in urine peak flow rate in 21, 31, and 36% of patients. The differences in efficacy parameters between the tamsulosin and placebo groups were determined to be statistically significant. In the extension of this study (n=418), benefits of tamsulosin were maintained and therapy was well tolerated. In the placebo group, a significant improvement in symptom score from baseline, but not in peak urine flow, was observed.

A Cochrane meta-analysis evaluated 14 studies (including the ones reviewed above), ranging in duration from 4-26 weeks, involving 3,418 men (45 to 85 years, mean age 64 years), with lower urinary tract symptoms (LUTS) secondary to BPH. A small to moderate improvement in LUTS and peak urine flow was provided by tamsulosin therapy, relative to placebo; tamsulosin 0.4 mg and 0.8 mg daily produced a 12% and 16% improvement in symptom score, respectively; both doses produced a mean increase from baseline in peak urine flow of 1.1 mL/sec.

Clinical course: Rapid onset of therapeutic effect, with improved maximum urinary flow rate beginning as early as the first day, and reduced subjective symptoms within the first week. One-third of men will not experience significant symptom reduction. Although mean changes in quality of life assessments have been reported to be greater with tamsulosin compared to placebo, blinded quality of life assessments by investigators have not found a statistically significant difference between tamsulosin and placebo. If no improvement in symptoms occurs after a 4-

6 week trial, treatment should be discontinued. Long-term data are limited, but open-label studies of 4-8.5 years duration reveal sustained efficacy and safety of chronic therapy. The long-term risk of acute urinary retention or need for prostatic surgery is not reduced; however, the time to the development of acute urinary retention is delayed.

Place in therapy
Pharmacological intervention is not as effective as surgery for relieving the symptoms of LUTS associated with BPH, but can provide adequate symptom control with a lower risk of adverse events. Efficacy does not appear to be affected by age, the presence of diabetes mellitus, or cardiovascular, neurological, or psychiatric comorbidity.

Alpha-adrenergic antagonists are usually used for the initial medical management of LUTS in BPH because of a quicker onset of effect and a more favorable side effect profile, compared to the 5-alpha-reductase inhibitors, which may require treatment for up to 6 months for effects to become clinically apparent. However, in patients with severe symptoms due to an enlarged prostate, initial therapy with a 5-alpha-reductase inhibitor may be utilized to reduce the size of the prostate. The 2003 American Urological Association guidelines for the management of BPH, and a meta-analysis reviewing the efficacy and safety of alpha-adrenergic antagonists used for treatment of LUTS suggestive of BPH published in 2004, conclude that alfuzosin, doxazosin, terazosin and tamsulosin have comparable efficacy.

Combination therapy with a 5-alpha-reductase inhibitor may be more effective than alpha adrenergic blocker monotherapy for LUTS associated with demonstrable prostatic enlargement and higher PSA values (one clinician suggests prostatic volume > 30 grams and a PSA level > 1.6 ng/mL), or in those patients with a higher risk of disease progression. At present, the best-tested combination is doxazosin and finasteride. The safety and efficacy of concurrent therapy with tamsulosin and finasteride has not been studied.

Advantages
- Once daily dosing, compared to terazosin, which is often administered twice daily; promotes treatment compliance.
- Does not require dosage titration upon initiation of therapy, as is necessary with the second generation, nonselective alpha-1 adrenergic blockers and alfuzosin, to minimize the risk of first-dose orthostatic hypotension; therefore, may provide more rapid symptom relief compared to agents which must be initiated with a subtherapeutic dose and titrated to a therapeutic dose.
- Compared to the second generation, nonselective alpha-1 adrenergic blockers (doxazosin, prazosin, terazosin), and to the selective alpha-1 adrenergic blocker, alfuzosin, unlikely to cause cardiovascular adverse effects; has a lower potential to produce hypotension or exacerbate the effects of concurrently administered antihypertensive agents; may be better tolerated in very elderly or hypertensive patients, or those with cardiovascular comorbidity. In one study evaluating patients with coexisting hypertension receiving atenolol, enalapril or nifedipine, co-administration of tamsulosin did not alter blood pressure, pulse rate, Holter monitoring or ECG results.

Disadvantages
- Compared to the use of nonselective alpha-1 adrenergic blockers, a higher probability of ejaculatory dysfunction exists (see SIDE EFFECTS).

Other uses
- In male and female patients: used as adjunctive therapy in ureterolithiasis to manage ureteral colic and hasten expulsion of kidney stones; initial data suggests benefit in the treatment of neurogenic lower urinary tract dysfunction.
- In male patients, limited evidence suggests possible benefit in the treatment of: orgasm-associated pain; chronic abacterial prostatitis or prostatitis/chronic pelvic pain syndrome (no benefit in one study of patients with refractory, chronic illness); LUTS associated with BPH, to achieve an early response in patients undergoing transurethral microwave thermotherapy (TUMT) (which may not be maximally effective for 3-6 months post-procedure); acute urinary retention (AUR) secondary to BPH; and painful ejaculation and urinary hesitancy associated with reboxetine therapy. Used in a limited numbers of patients to prevent postoperative urinary retention following: removal of the urinary catheter after radical retropubic prostatectomy; and lower gastrointestinal surgery in LUTS/BPH patients. Has been used prophylactically in small numbers of patients to decrease morbidity associated with prostate-directed therapies including TUMT, radiotherapy, brachytherapy, and transrectal ultrasound-guided biopsy of the prostate.
- In pediatric patients, has been used in a limited number of patients for the treatment of primary bladder neck dysfunction.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindications

- **Hypersensitivity** to tamsulosin or any component of the drug product.

Precautions

- **Carcinoma of the prostate**, and other conditions displaying symptoms similar to BPH, should be excluded prior to initiating therapy
- **Should not be used as an antihypertensive agent**; does not produce a clinically significant reduction of blood pressure. Risk of orthostatic hypotension, including first-dose syncope, is low.
- Although this agent is a sulfamoylphenethylamine derivative, incorporating a sulfonamide-like chemical structure, it does not contain an arylamine group, which is hypothesized to be critical in the production of a hypersensitivity reaction. **Cross-allergenicity is unlikely**; no reports of cross-sensitivity with sulfonamides exist.
- Safety and efficacy not established in **women** and **children**.
- In **elderly** male patients, the development of a new complication of cataract surgery, the intraoperative floppy iris syndrome, is thought to be associated with the use of tamsulosin; some ophthalmologists suggest that this agent be discontinued for 2 weeks prior to cataract surgery, although the benefit of discontinuation of therapy prior to surgery in unknown. In a few cases of the development of this adverse effect, the drug had been discontinued for periods from 5 weeks to 9 months.
- **Report** any unexpected or serious reactions to Health Canada's adverse reaction monitoring program (toll free telephone 1-866-234-2345, toll free fax 1-866-678-6789).

PREGNANCY AND LACTATION

Studies in rats and rabbits have shown no adverse effects on fetal development. Administration to male and female rats has produced impairment of fertility; the effect in males may be due to impaired ejaculation. No published data exist regarding effects on human fertility, pregnancy, or lactation.

SIDE EFFECTS

Frequency of occurrence in excess of that observed with placebo is indicated in brackets. Incidence of adverse events and treatment withdrawal are dose-dependent; the incidence of "any" adverse event (in excess of that with placebo therapy) is reported to occur in 6% and 14% of men receiving 0.4 mg and 0.8 mg daily, respectively. A meta-analysis of 14 clinical studies, reported rates of "all cause" treatment withdrawal with tamsulosin 0.2 mg and 0.8 mg daily as 6.5% and 16.3%, respectively.

Adverse effects are generally mild; most frequently reported adverse events are dizziness, rhinitis and abnormal ejaculation. Although the development of ejaculatory dysfunction exists, the degree to which this possible adverse effect interferes with sexual function is unclear; discontinuation of therapy because of the development of this adverse effect has been reported in fewer than 1% of patients when all studied dosages are considered and 1.2% of patients with administration of 0.8 mg daily. Assessment of patients receiving tamsulosin or alfuzosin in one study (n=256) revealed no significant difference between treatments regarding effect on sexual function scores.

Does not appear to have any significant effect on prostate-specific antigen levels, urinalysis, or routine biochemical and hematological tests.

Cardiovascular: Asymptomatic hypotension (6.6%); symptomatic postural hypotension (0.4% and 0.8% with 0.4 mg and 0.8 mg daily, respectively); syncope (rare); palpitations (infrequent).
CNS: Asthenia (2-4% and 3-6% with 0.4 mg and 0.8mg daily, respectively); dizziness (5% and 8% with 0.4 mg and 0.8mg daily, respectively); somnolence (1% and 5% with 0.4 mg and 0.8mg daily, respectively); vertigo (0.3%); headache (1.7%).
Gastrointestinal: Nausea, vomiting, diarrhea, constipation (occasional); life-threatening chemical erosive esophagitis with esophageal occlusion (1 case, to date).
Genitourinary: Abnormal ejaculation (includes retrograde ejaculation, ejaculation failure and decreased volume of ejaculate; reversible upon withdrawal of therapy) (10% and 26% with 0.4 mg and 0.8 mg daily, respectively; 30% with chronic administration); erectile problems (0.9%); priapism (rare), probably less than 1 in 50,000 patients).
Ocular: Intraoperative floppy iris syndrome (at least 25 cases, see CONTRAINDICATIONS AND PRECAUTIONS).

Other: Nasal symptoms, including rhinitis (4.8% and 9.6% with 0.4 mg and 0.8 mg daily, respectively). Allergic-type reactions, with positive rechallenge in some cases, have included: skin rash, pruritus, urticaria (occasional); angioedema of the tongue, lips and face (rare).

INTERACTIONS
Primarily metabolized by CYP2D6 and CYP3A4, while other CYPs may be involved to a minor extent; inhibitors of these CYP450 enzymes may increase drug levels and effects; inducers of these CYP450 enzymes may decrease drug levels and effects. Due to the various metabolic pathways involved, this agent is probably less susceptible to interaction with a drug which affects a single CYP enzyme.

No drug interaction reported when co-administered with atenolol, digoxin, dutasteride, enalapril, furosemide, nifedipine, sildenafil, theophylline, tadalafil, or vardenafil.

DRUG	EFFECT	MECHANISM	IMPORTANCE
Alpha-1 adrenergic antagonists	Possible hypotension	Additive	Caution
Cimetidine	Increased plasma levels of tamsulosin	Decreased metabolism of tamsulosin	Clinical significance unknown; caution with doses of tamsulosin > 0.4 mg daily
Warfarin	Altered effectiveness of either drug	CYP450-related	Caution; limited and inconclusive data; monitor PT and INR

DOSAGE
Benign Prostatic Hyperplasia: Dosage titration not required upon initiation of therapy. Should be administered 30 minutes following the same meal each day to provide consistent plasma levels.
Adults: 0.4 mg daily. If inadequate clinical response to 0.4 mg daily after 2 to 4 weeks, dosage may be increased to 0.8 mg daily. If therapy is discontinued or interrupted for several days, treatment should be restarted with 0.4 mg daily. In a study involving a small number of patients, maintenance therapy with 0.4 mg every other day was found to be as effective as 0.4 mg daily.

Ureterolithiasis, to manage ureteral colic and hasten expulsion of kidney stones:
Adults: 0.4 mg daily for up to 28 days, or until kidney stone passes.

Elderly: No adjustment required.

Hepatic impairment: No adjustment required in mild to moderate dysfunction.

Renal impairment: No adjustment required for creatinine clearance > 10 mL/min.

NURSING IMPLICATIONS
Tamsulosin capsules are a sustained release formulation, which must be swallowed whole, and must not be crushed, opened or chewed.

Administering this medication 30 minutes following the same meal every day produces consistent plasma levels. To ensure passage through the esophagus, it should be given with an adequate amount of fluid, and not administered while the patient is lying down.

Some patients may develop orthostatic hypotension and complain of feeling lightheaded or dizzy, particularly following initiation of therapy or following an increase in dosage. Assist ambulation to avoid falls in patients with these complaints. To decrease these effects, advise patients to rise slowly from sitting or lying positions.

Prompt medical attention must be sought for a painful or persistent penile erection, to avoid permanent inability to achieve to an erection. This side effect occurs rarely.

In patients who are to undergo cataract surgery, inform the physician that this medication is being administered. Some cases of an intra-operative complication, floppy iris syndrome, have occurred during this type of surgery in patients taking this medication.

PATIENT INSTRUCTIONS

Tamsulosin (tam-soo-loh-sin) is used to treat the symptoms of an enlarged prostate, a common condition in men over the age of 50 years, which causes problems with urination. It may be prescribed for other conditions including bladder problems, in both males and females.

Capsules must be swallowed whole, and must not be crushed, opened or chewed. Take this medication 30 minutes following the same meal each day. Do not take this medication while lying down.

If you forget to take a dose, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take a double dose to make up for a missed dose. If you miss doses for several days, consult your physician before restarting this medication, especially if you are taking more than one capsule daily.

This medication may cause dizziness if you suddenly get up from sitting or lying down. Getting up slowly may help to lessen the dizziness.

If dizziness occurs, avoid driving or any potentially hazardous tasks for 12 hours after taking the first dose, or following an increase in dose. Other side effects include problems involving ejaculation, and stuffy or runny nose. If a rash occurs, stop taking this medication and consult your physician.

This medication rarely cause a prolonged, painful erection of the penis, which is unrelieved by sexual intercourse or masturbation. Medical attention should be sought for this problem as soon as possible, since if left untreated, it can lead to a permanent lack of the ability to have an erection.

If you are to undergo cataract surgery, inform the physician that you are taking this medication. Some cases of an unusual complication have occurred during this type of surgery, in patients taking this medication.

Store this medication in a labeled container, away from heat, light and moisture, and out of the reach of children.

If you have experienced an unexpected or serious reaction to this medication, this can be reported to Health Canada's monitoring program (toll free telephone 1-866-234-2345, toll free fax 1-866-678-6789). Note that this is not an emergency number.

PRESENTATION

Capsules, sustained release: 0.4 mg.

References are available on request.