# Tamsulosin oral controlled absorption system (OCAS) in the treatment of benign prostatic hypertrophy

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**Abstract:** The efficacy of tamsulosin at the cost of a relatively benign side effect profile has been attributed to receptor selectivity directed at the $\alpha_{1a}$ and $\alpha_{1d}$ adrenergic receptor subtypes. The oral-controlled absorption system (OCAS®) represents a drug delivery refinement that incorporates a matrix of gel-forming and gel-enhancing agents to promote a constant drug release independent of environmental food or fluid. There are clinical data to support the concept that drug peaks are lessened and that drug release continues throughout the alimentary tract due to the OCAS formulation. Furthermore this equates with less adverse effects on physiologic parameters. To date however improvements in cardiovascular symptoms such as dizziness, headache and syncope have not been demonstrated in healthy men. Ejaculatory dysfunction appears less problematic with the OCAS preparation. Tamsulosin OCAS may be of greatest benefit to men with cardiovascular co-morbidities taking anti-hypertensive medications that might predispose them to symptomatic hypotensive episodes. It will be necessary to evaluate this group of men more closely in further trials to determine what they stand to gain from changing medications, and then relate this to drug costs to draw a final conclusion as to the place of tamsulosin OCAS in contemporary urological practice.

**Keywords:** lower urinary tract symptoms, benign prostatic hyperplasia, tamsulosin OCAS, safety, efficacy, tolerability

## Introduction

Lower urinary tract symptoms (LUTS) are an increasing quality of life issue for many men as they age. Roughly one quarter of men over the age of 45 are effected by LUTS as defined by an International Prostate Symptom Score (IPSS) greater than 7, and the prevalence in men over the age of 70 is closer to 40% (Andersson et al 2004).

The approach to treatment of these symptoms has always been grounded in the analysis of risk versus benefit for the individual. Historically symptoms have been managed by conservative measures such as fluid intake modification or poorly substantiated remedies from the general consciousness until symptoms progressed to the point where the risks of surgery were considered acceptable to achieve the benefits of symptom relief. Many men tolerated profound difficulties for fear of the surgeon's blade. This has been revolutionized by the development of effective medical therapy. Medical treatment for LUTS attributed to benign prostatic hyperplasia (BPH) has now become the mainstay of treatment due to the non-invasive nature and reversibility it offers. Surgical intervention is now generally reserved for progressive disease or failures of medical therapy. Current thought holds that lower urinary tract symptoms arise at least in part from outflow tract obstruction. This then provokes physiological and behavioral changes in bladder function. Outflow obstruction is considered as the sum of two contributing parts, one dynamic and one static. Medical therapy has evolved to address both contributory components with α adrenergic receptor antagonists used as

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primary treatment for the former and 5 α reductase inhibitors used for the latter. The α adrenergic receptor antagonists work primarily by reducing smooth muscle tone in the bladder neck and prostate whereas 5 α reductase inhibitors induce epithelial atrophy (Gup et al 1990; Lepor 1990; Gormley et al 1992). A combination of the two has been shown to be superior to either alone in achieving long-term prevention of disease progression; however, it is clear that reduction of prostate volume is not always required to achieve improvements in symptomatology (McConnell et al 2003).

For the great majority of men, BPH is a disease of symptoms rather than complications and therefore any medical treatment for this condition must achieve symptom relief with minimal toxicity. Although α blockers have been regarded as an effective therapy option for some time, they are not without side effects (Roehrborn and Siegel 1996). Recently attempts have been made to improve the therapeutic window of these agents with modifications aimed at increasing receptor selectivity and optimizing drug delivery. This article is intended to review the role of tamsulosin oral-controlled absorption system (OCAS®). This represents a novel drug delivery system for the $\alpha_1$-adrenergic receptor specific tamsulosin, in the treatment of LUTS related to BPH.

## Tamsulosin

It was recognized as early as the mid 1970s that subgroups of α adrenergic receptors exist (Langer 1974). Phenoxybenzamine, the original non-selective α receptor antagonist used for the treatment of LUTS, induced significant side effects such as fatigue, impaired ejaculation, nasal congestion, dizziness, and hypotension. The discovery of an abundance of the $\alpha_1$ receptor subgroup in the bladder neck and prostatic smooth muscle, coupled with the need to avoid these side effects, drove research into the concept of uroselectivity in which refinement of receptor stimulation reduces collateral side effects (Lepor et al 1988). Prazosin, the first $\alpha_1$ selective agent, demonstrated comparable efficacy with improved tolerability by comparison with phenoxybenzamine. Longer-acting $\alpha_1$ selective medications followed shortly thereafter. Among these was tamsulosin, the first $\alpha_1$ subtype selective antagonist. The $\alpha_{1a}$ and to a lesser extent $\alpha_{1d}$ receptors predominate in urologic tissues, whereas $\alpha_{1b}$ receptors are found more commonly in the cardiopulmonary, splenic, renal, and vascular tissues (Roehrborn and Schwinn 2004). Tamsulosin has a roughly 10 times higher affinity for the $\alpha_{1a}$ than the $\alpha_{1b}$ receptor (Kenny et al 1996).

Phase III randomized placebo controlled trials have demonstrated clinically significant improvements in symptom scores and peak flow rates at both 0.4 mg and 0.8 mg doses of tamsulosin (Lepor 1998; Narayan and Tewari 1998). Subsequently a systematic review of clinical trials has reached similar conclusions (Wilt et al 2002). The weighted mean difference in change from baseline symptom score for tamsulosin (0.4 mg) over placebo was 12% and the weighted mean difference in change from baseline peak urinary flow rate for tamsulosin (0.4 mg) over placebo was 1.05 mL/s (95% CI 0.59–1.51) (selected trials are summarized in Table 1). Overall there was a 5% adverse event related withdrawal rate on the 0.4 mg dose schedule. The predominant side effects were dizziness, rhinitis, abnormal ejaculation, and headache, each of which occurred in 6%–10% of participants (Table 2). The Cochrane Database review of 2003 stated that tamsulosin provided moderate benefits in urinary symptoms and flow rate compared with placebo at a level similar to other alpha antagonists (Wilt et al 2003). Additionally there were minimal improvements in symptomatology but substantial increases in side effects when the dose of tamsulosin was increased from 0.4 mg to 0.8 mg.

A multicenter extension trial involving participants from three shorter double blind placebo-controlled studies was published in 2003 (Narayan et al 2003). Of the 609 men recruited, 109 completed the 6-year follow-up (as only 159 men had

**Table 1** Selected randomized placebo controlled trials of tamsulosin (0.4 mg) assessing symptom scores (recorded as the percentage change between mean baseline and mean achieved symptom scores) and maximal flow rates (recorded as the percentage change between mean baseline and mean achieved peak flow in milliliters per second)

| Reference | Number | Duration | % change in symptom score tamsulosin | % change in symptom score placebo | p value | % change in mean peak flow (mL/s) tamsulosin | % change in mean peak flow (mL/s) placebo | p value |
|---|---|---|---|---|---|---|---|---|
| Abrahms et al 1997 | 126 | 14/52 | –29 | –18 | 0.002 | 22 | –1 | 0.03 |
| Chapple et al 1996 | 575 | 14/52 | –35 | –26 | N.S. | 16 | 6 | 0.002 |
| Lepor et al 1998 | 756 | 17/52 | –41 | –28 | <0.001 | 24 | 9 | <0.001 |
| Narayan and Tewari 2003 | 735 | 17/52 | –27 | –19 | 0.01 | 15 | 9 | NS[a] |

[a]Not significant.

**Table 2** Adverse event profile summarized from multiple randomized controlled trials (derived from Wilt et al 2002)

| Adverse event | Tamsulosin | Placebo | Relative risk[a] |
|---|---|---|---|
| Withdrawal – all cause | 12.2% | 12% | 1.02 (0.80–1.30) |
| Withdrawal – due to adverse event | 7.2% | 6.7% | 1.08 (0.72–1.62) |
| Headache | 14.3% | 14.6% | 1.00 (0.81–1.23) |
| Dizziness | 11.9% | 7.8% | 1.50 (1.13–1.98) |
| Rhinitis | 11.2% | 6% | 1.84 (1.24–2.72) |
| Abnormal ejaculation | 10.8% | <1% | 17.0 (2.5–114.2) |
| Asthenia | 6% | 4.3% | 1.33 (0.89–1.97) |
| Any adverse event | 53.5% | 51.3% | 1.07 (0.72–1.62) |

[a]Relative risk is expressed as the calculated value with 95% confidence intervals in parentheses.

received 2 years or more of treatment prior to entry). A 25% or greater decrease in AUA score was preserved for up to 80% of men and a 30% or better improvement in maximal flow rate was sustained for up to 40% of men. Fifteen percent of patients discontinued tamsulosin due to side effects, including 0.2% each for postural hypotension and syncope. This study indicates that the early efficacy and tolerability of tamsulosin continues beyond 5 years for most men.

How can we improve on tamsulosin in the treatment of BPH related LUTS? Symptom control increases somewhat with dose escalation; however, the cost in terms of side effects is disproportionate (Wilt et al 2002). The concept of prolonging the optimal serum drug level to achieve a longer effect for each dose taken is an appealing one. Theoretically it might also dampen adverse events resulting from rapid drug peaks soon after ingestion. The mode of drug delivery therefore presents a target for refinement.

The conventional modified release (MR) formulation of tamsulosin has a variable absorption profile dependent on when it is taken in relation to food and gastrointestinal transit time. As such if 0.4 mg is taken on an empty stomach it results in a roughly 70% higher serum level than if taken after a meal (Lyseng-Williamson et al 2002). Taking tamsulosin in the fasting state increases the risk of unwanted cardiovascular effects such as orthostatic hypotension, dizziness, headache, and syncope (Michel et al 2005a). Additionally the multi-coated membrane of the pellet releases drug only in the presence of water which is progressively less available along the alimentary canal. This results in the release of drug largely in the stomach and small intestine rather than the colon (Chapple and Chartier-Kastler 2006). These drawbacks in combination lead to suboptimal serum drug levels over the 24-hour dosing interval which may correlate with poorer symptom control, and a reliance on patient compliance with respect to timing to lessen side effects.

## Tamsulosin oral controlled absorption system

Repackaging tamsulosin in the OCAS formulation arose from a desire to extend drug release over a longer period of time. Optimal serum and tissue drug levels might be expected to lead to a subsequent improvement in symptom control, especially overnight. The OCAS construct uses gel-forming and gel-enhancing agents to overcome the continual dependence of previous drug delivery systems on water to enable chemical release. The matrix hydrates rapidly in the stomach and thereafter is no longer dependent on environmental water for drug release. It is also resistant to changes in pH and gastrointestinal motility (Sako et al 1996). Theoretically this system should decrease food effect and reduce peak to trough serum drug fluctuations, maintaining concentrations above the minimum effective level for longer and blunting the degree and rapidity of maximal levels.

Randomized phase one studies have been conducted to determine whether this in fact is the case (Michel et al 2005a). In each, healthy volunteers between the ages of 19 and 44 were given tamsulosin OCAS, and serum levels assessed before then and at intervals after dosing to determine the pharmacokinetic profile.

The first study compared 0.4 mg tamsulosin MR in the fed state with 0.4 mg tamsulosin OCAS in the fasted state (Michel et al 2005b). The maximal serum concentration achieved ($C_{max}$) and peak to trough variations (expressed as maximal concentration divided by the concentration at 24 hours ($C_{24hr}$) were reduced in the OCAS group. Effects on time to maximal concentration and the elimination half-life of the drug were similar with each formulation however the area under the curve for the 24-hour period was slightly less with the OCAS preparation. The trade-off between the preparations for steadier drug delivery and avoidance of food effect is a somewhat lower total amount of drug absorbed for the same dose administered (Table 3).

**Table 3** Pharmacokinetic outcomes of the randomized comparison of 0.4 mg of tamsulosin in modified release (MR) form in the fed state with oral-controlled absorption system (OCAS) form in the fasting state (derived from data of Wilt et al 2002)

| Variable | Tamsulosin MR 0.4 mg | Tamsulosin OCAS 0.4 mg |
|---|---|---|
| $C_{max}$ (ng/mL) | 13.74 | 5.88 |
| $T_{max}$ (h) | 6.67 | 8.51 |
| $T_{1/2}$ (h) | 16.13 | 18.67 |
| AUC (ng.h/mL) | 253.7 | 175.7 |

The second study looked at tamsulosin 0.4 mg, 0.8 mg, and 1.2 mg doses and the effect of food on drug delivery (Wilt et al 2002). No difference was observed in relation to serum drug levels dependent on whether volunteers were fed or not at the time of drug administration. Increasing doses led to increased $C_{max}$ and AUC but not $T_{max}$ or $T_{1/2}$. The authors concluded that OCAS delivery resulted in a more favorable pharmacokinetic profile than MR delivery and was independent of food consumption.

Further studies using scintigraphically measured technetium-99m labeled tamsulosin OCAS release have confirmed continuous drug release throughout the entire alimentary tract, independent of regional transit times (Stevens and Speakman 2006).

## Efficacy of tamsulosin OCAS

Demonstration of a favorable pharmacokinetic profile in phase I studies allowed progression to phase II and III trials to evaluate whether improvements in efficacy would follow (Chapple et al 2005a, b; Djavan et al 2005).

Chapple et al (2005a) published a study of 839 men 45 years of age or older with International Prostate Symptom Scores (IPSS) greater than 12, in which subjects were randomized to tamsulosin OCAS 0.4 mg, 0.8 mg, or 1.2 mg doses or placebo. All doses of tamsulosin OCAS reached statistical significance for improvement in total IPSS (of ≥25%) and in the IPSS quality of life question alone over placebo (Table 4). There was a 10% increase from 63% (placebo) to 73% (0.4 mg dose) in the number of men treated who had a response in IPSS. Whether this is clinically significant is open to debate. The study did demonstrate that although there was no clear treatment benefit with doses higher than 0.4 mg, there was a clear increase in treatment-related adverse effects and thereby established the optimal treatment dose.

A further phase III trial involving 2152 men compared the symptomatic response to placebo, tamsulosin MR 0.4 mg, tamsulosin OCAS 0.4 mg, or 0.8 mg (Chapple et al 2005b). Findings were similar to the abovementioned trial in terms of relative improvements from the tamsulosin OCAS 0.4 mg and 0.8 mg doses (Table 5). Adverse events were similar for each as well. Of particular interest are the almost identical response and side effect profiles of the OCAS and MR delivery systems at the 0.4 mg dose. The authors commented that the adverse event rates probably under estimate the real life clinical situation regarding the MR formulation. They suggested that compliance with drug dosing in relation particularly to food consumption in the trial was much higher than might be expected in general practice and also pointed out that those with significant cardiovascular co-morbidities were excluded by the trial protocol.

It seems increasingly clear that relief of storage symptoms has a more profound effect on overall quality of life than relief of voiding symptoms. Nocturia, being woken by the need to void, appears particularly bothersome for many men as loss of sleep may be reflected in daytime sleepiness, impaired reaction time and mood change (Stanley 2005). Improving sleep duration and quality is certainly a reasonable goal of BPH-related LUTS treatment and in an attempt to address this a randomized, placebo-controlled trial involving 117 men looked at hours of undisturbed sleep (HUS) as an outcome variable (Djavan et al 2005). The results of this ambitious study are presented in Table 6, but essentially the authors confirmed symptomatic improvements with tamsulosin OCAS over placebo in line with previous studies. There were no significant differences in the number of nocturia events or minutes of undisturbed sleep. The study is most interesting for its attempt to quantify the benefit of medical therapy of LUTS on sleep and represents a pioneering foray into this field, worthy of future refinement. It does not however provide evidence to support the superior efficacy of the OCAS formulation over other drug delivery systems for this purpose.

**Table 4** Symptomatic response and adverse event rates in men on various doses of tamsulosin oral-controlled absorption system or placebo (derived from data of Chapple et al 2005a)

| | Placebo | 0.4 mg | 0.8 mg | 1.2 mg |
|---|---|---|---|---|
| Number of subjects | 211 | 203 | 206 | 210 |
| Percent with reduction in IPSS ≥25% | 63% | 73% | 80% | 77% |
| P value (treatment vs. placebo) | | 0.02 | <0.01 | 0.02 |
| Change in IPSS QoL score | −0.9 | −1.3 | −1.4 | −1.4 |
| P value (treatment vs placebo) | | 0.0005 | <0.0001 | <0.0001 |
| Adverse events | 26% | 29% | 30% | 36% |

**Abbreviations:** ICSS, International Prostate Symptom Score.

**Table 5** Symptomatic responses and adverse event rates in men on placebo, tamsulosin oral-controlled absorption system (OCAS) or modified release (MR) drug delivery systems (derived from data of Chapple et al 2005b)

| | Placebo | OCAS 0.4 mg | OCAS 0.8 mg | MR 0.4 mg |
|---|---|---|---|---|
| Number | 350 | 354 | 707 | 700 |
| Percent with reduction in IPSS ≥25% | 60.9% | 71.2% | 75.4% | 73.8% |
| Change from baseline IPSS | –3.7 | –4.7 | –5.0 | –5.0 |
| P value (treatment vs placebo) | | <0.001 | | <0.001 |
| P value (treatment vs MR 0.4 mg) | | | NS[a] | |
| Change in IPSS QoL score | –2.2 | –3.0 | –3.0 | –3.0 |
| P value (treatment vs placebo) | | <0.001 | | <0.001 |
| P value (treatment vs MR 0.4 mg) | | | NS | |
| Adverse events | 3.7% | 6.9% | 11.1% | 7.8% |

[a]not significant.
**Abbreviations:** ICSS, International Prostate Symptom Score.

## Cardiovascular safety of tamsulosin OCAS

Blockade of $\alpha_1$ adrenergic receptors with antagonists allows smooth muscle relaxation in the prostate, bladder neck, and urethra; however, inhibition of the same receptors in vascular smooth muscle leads to vasodilatation and lower blood pressure. In most men this is of no consequence, in some it may induce symptomatic results such as dizziness, headache, and syncope. As a large number of men requiring treatment for BPH-related LUTS are elderly with cardiovascular comorbities and frequently on medications with antihypertensive effects they represent the highest risk group for α blocker induced cardiovascular side effects. Normal functional reserves may be further compromised by times of relative cardiovascular stress such as heavy meals, exercise, hot conditions, and dehydration (Barendrecht et al 2005).

Using phenylephrine an $\alpha_1$ adrenergic receptor agonist, Michel et al (2005c) attempted to determine the likelihood that tamsulosin OCAS would cause adverse cardiovascular events. They reasoned that the more phenylephrine required to increase diastolic blood pressure (dBP) and total peripheral resistance (TPR), the greater effect the $\alpha_1$ adrenergic receptor agonist is having on the peripheral vasculature and therefore the more likely it is to cause cardiovascular side effects at times of limited reserve. This study used 18 healthy men younger than 45 years of age as subjects for a 3-way crossover study that compared placebo with the tamsulosin OCAS and MR formulations. In order to anticipate real world non-compliance with dosing instructions (which suggest that the MR form should be taken after breakfast) the drugs were given in the fasting state. Phenylephrine induced changes in dBP and TPR were measured 2 hours prior to, then every 2 hours after, dosing over a 10-hour period. There was less inhibition of phenylephrine induced changes in dBP and TPR with the post dose OCAS formulation than seen with the MR formulation and this was statistically significant in all except the initial 2-hour post-dose interval. The authors interpreted these statistical changes in physiological parameters to represent a better cardiovascular safety profile for the former preparation.

To assess the clinical relevance of these findings, the same authors measured the effects of the two formulations on 40 healthy older (≥60 years old) men using orthostatic stress testing (Michel et al 2005d). This involved subjects lying down for 5 minutes, then sitting for 2 minutes, and finally standing for 3 minutes while non-invasive pulse and blood pressure measurements were conducted at 2-hourly intervals over 10 hours following dosing in the fasted state. Positivity was indicated by one or more of (1) symptoms (eg, dizziness, light-headedness), (2) a decrease in sBP ≥20 mmHg, (3) a decrease of dBP ≥10 mmHg or a standing dBP <60 mmHg, (4) an increase in pulse rate ≥20 beats/minute or a standing pulse rate ≥100 beats/minute. The OCAS formulation had a cumulative incidence of positive tests of 17.5% compared with 31.7% for the MR formulation with

**Table 6** Symptomatic responses and sleep change with tamsulosin oral-controlled absorption system (OCAS) 0.4 mg compared with placebo (derived from data of Chapple et al 2005b).

| | Placebo | Tamsulosin OCAS 0.4 mg | p value |
|---|---|---|---|
| Baseline IPSS | 18.1 | 18.2 | NS[a] |
| Change in IPSS | –5.6 | –8.0 | <0.01 |
| Change in nocturia | –0.7 | –1 | 0.09 |
| Change in HUS | 60 minutes | 81 minutes | 0.20 |

[a]not significant.
**Abbreviations:** HUS, hours of undisturbed sleep; ICSS, International Prostate Symptom Score.

the greatest difference being at 4 hours post dose (difference of 20%). At each time point there were fewer positive tests in the OCAS arm and the results were statistically significant. Although there was little difference between the two preparations in terms of symptomatic adverse events (17.5% with OCAS, 22.5% with MR), the authors stressed that the trial subjects were healthy and that these results would likely underestimate differences for the general population at higher risk of cardiovascular adverse events.

The same principles were applied to a further trial comparing 0.4 mg tamsulosin OCAS with 10 mg alfuzosin XL (Michel and Chapple 2006). In this two-part study, the above methods were again applied. Phenylephrine was administered to 18 healthy young (≤45 years old) volunteers and orthostatic stress testing was conducted on 40 healthy older men (≥60 years old). There were statistically significant reductions in phenylephrine inhibition favoring tamsulosin OCAS at the 2- and 4-hour dose intervals. The proportion of positive orthostatic tests was higher in the alfuzosin group overall (17.5% vs 5%) and at each time interval with the greatest difference (17.5%) at the 6-hour post-dose interval. Almost all differences were demonstrated in changes in blood pressure with pulse rate and symptomatic events being comparable between the two drugs.

Taken together these studies indicate that the OCAS form of tamsulosin shows less inhibition of vascular $\alpha_1$ adrenergic receptors than tamsulosin MR or alfuzosin XL and that this translates into a modest reduction in disruption of cardiovascular physiological response measures to exercise in healthy volunteers. The previously mentioned phase III of over 2000 men did not show a significant difference in blood pressure changes or symptoms attributable to cardiovascular consequences, between tamsulosin OCAS and placebo (Stanley 2005). However, the trial was not designed or powered to evaluate differences in adverse events between the groups. Whether the findings from these trials may be extrapolated to the general patient group at higher risk of such sequelae with treatment is open to speculation, as to date this has not been assessed.

## Tolerability of tamsulosin OCAS

Generally speaking factors affecting the tolerability of tamsulosin may be considered in two broad categories, one related to cardiovascular function, the other to sexual function. The $\alpha_1$ adrenergic receptor antagonists as a class appear to lack major effects on sexual desire and reports of their effects on erectile function have been mixed (van Dijk et al 2006). Ejaculatory dysfunction, however, has been more clearly demonstrated in a number of randomized controlled trials (van Dijk et al 2006). Within the drug class, numerically higher incidences have been seen with tamsulosin compared with other $\alpha_1$ blockers, although in most studies this has failed to achieve statistical significance (Narayan et al 2005; Nordling 2005). As it has been estimated that more than half of men over 60 years of age have some abnormality of ejaculatory function, the relevance of this cluster of side effects is perhaps less than that of cardiovascular adverse events (Frankel et al 1998).

The primary objective of the phase III trial of tamsulosin OCAS was to evaluate treatment effect on LUTS, as such the study detailed adverse effects with descriptive statistics only (Table 7). The exception to this was an analysis of the two most commonly reported adverse events, abnormal ejaculation and dizziness. In this, ejaculatory dysfunction was seen statistically more frequently in the tamsulosin MR 0.4 mg group than placebo (p = 0.014) but there was no difference

**Table 7** Adverse events with tamsulosin in varying formats and doses as reported by Chapple et al (2005b)

| | Placebo | OCAS 0.4 mg | OCAS 0.8 mg | MR 0.4 mg |
|---|---|---|---|---|
| Number | 350 | 354 | 707 | 700 |
| One or more adverse events | 20% | 26% | 27% | 24% |
| One or more treatment related adverse events | 7% | 11% | 14% | 12% |
| Cardiovascular events | 2.2% | 2.5% | 3.9% | 3.2% |
| Dizziness | 1.4% | 1.4% | 2.4% | 1.3% |
| Abnormal ejaculation | 0.3% | 1.9% | 5.3% | 3.1% |
| Number with CVS information | 340 | 344 | 690 | 691 |
| Change in mean sBP[a] on standing | –1.5 | –2.2 | –3.5 | –3.5 |
| Change in mean dBP on standing | –1.2 | –0.5 | –2.1 | –2.2 |
| Discontinuation due to adverse events | 0.6% | 1.9% | 2.4% | 1.3% |

[a]blood pressure changes are orthostatic, measured on standing in mmHg with changes between baseline and at 12 weeks.
**Abbreviations:** dBP, diastolic blood pressure; sBP, systolic blood pressure; CVS, cardiovascular system.

between placebo and the tamsulosin OCAS 0.4 mg group (p value not stated). The two formulations at the 0.4 mg dose were not compared with direct statistical analysis. Given that the absolute difference in adverse events was only 1.2%, this may not have reached statistical significance and is unlikely to represent a clinically significant finding.

Overall the incidence of adverse event related treatment withdrawals has been low, in the order of 2% or less, in each of the trials described previously. As a consequence both the oral controlled absorption system and modified release formulations may be considered to be well tolerated. The 0.4 mg dose in the OCAS preparation appears preferable to higher doses, given little difference in efficacy but a dose-response-related increase in adverse events, as demonstrated in the previously described phase II trial (Chapple et al 2005a).

## Conclusions

Medical therapy is now established as the first-line treatment for uncomplicated BPH related lower urinary tract symptoms and this currently includes either an $\alpha_1$ adrenergic receptor antagonist, a 5 $\alpha$ reductase inhibitor or a combination of both. Among the $\alpha$ blockers, tamsulosin has demonstrated efficacy in a number of randomized trials with some improvement in its relative side effect profile. This has been attributed to receptor selectivity directed at the $\alpha_{1a}$ and $\alpha_{1d}$ subtypes. Modifications in drug delivery such as with the OCAS have been sought to avoid the effects of food on drug serum peaks and therefore side effects and to prolong drug release regardless of gastrointestinal transit. This in turn may increase the length of time for which symptoms are better controlled.

Data to date support the concept that drug peaks are lessened and that drug continues to be released once it has passed into the colon despite a relative lack of water in this area. The 0.4 mg dose provides the most desirable therapeutic risk: benefit ratio. The current evidence suggests that the OCAS formulation is no worse than the MR formulation in achieving symptom control; however, the hoped-for improvements in nocturia control have not eventuated in clinical trials so far. In terms of side effects, physiologic parameters measured during orthostatic stress tests are less adversely affected by the OCAS formulation than the MR formulation taken in the fasting state and in comparison to alfuzosin XL 10 mg. This did not, however, translate into significant differences in cardiovascular side effects for healthy men taking the drugs. Ejaculatory dysfunction appears less likely with the OCAS preparation than the MR preparation of tamsulosin.

The role of tamsulosin OCAS in the treatment of BPH related LUTS is in evolution. For otherwise healthy men the benefits in terms of efficacy over the MR formulation appear negligible and the benefits in terms of side effects are modest. The drug delivery system places less importance on dose timing, reducing the importance of patient compliance in this regard. The OCAS formulation may be of greatest importance to those men with multiple medical and particularly cardiovascular co-morbidities taking anti-hypertensive medications that might predispose them to symptomatic hypotensive episodes. It will be necessary to evaluate this group of men more closely in further trials to determine what they stand to gain from changing medications, and relate this to drug costs before drawing a final conclusion as to the role of tamsulosin OCAS in contemporary urological practice.

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