Balancing clinical outcomes and quality of life aspects in the treatment of LUTS/BPH
van Dijk, M.M.

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Tamsulosin – modified release and oral controlled absorption system formulations in the treatment of benign prostatic hyperplasia

Marleen M. van Dijk¹, Jean J.M.C.H. de la Rosette¹, Martin. C. Michel²

¹ Department of Urology, Academic Medical Center, University of Amsterdam, the Netherlands
² Department of Pharmacology & Pharmacotherapy, Academic Medical Center, University of Amsterdam, the Netherlands

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a histological diagnosis. BPH itself may not cause any symptoms but frequently leads to benign prostatic enlargement which can cause bladder outlet obstruction and may be associated with bothersome lower urinary tract symptoms (LUTS). Such LUTS consist of obstructive/voiding symptoms (such as hesitancy, poor urinary flow, intermittent voiding and a sensation of incomplete emptying of the bladder) and irritative/storage symptoms (such as frequency, urgency and nocturia). Since on the one hand not all LUTS may be due to BPH and on the other hand the term BPH is frequently but incorrectly used as a synonym for a clinical condition, we will use the term LUTS/BPH in this manuscript to refer to the condition.

The prevalence of BPH increases with age, and ultimately almost each man will develop this histological diagnosis if living long enough. Clinically relevant LUTS/BPH occur less frequently than the histological diagnosis but nevertheless are present in about 30% of elderly males. LUTS/BPH are believed to involve two main factors: The enlarged prostate may cause a static obstruction, whereas contraction of prostatic smooth muscle may cause a dynamic obstruction.

OVERVIEW OF THE MARKET

LUTS/BPH can be treated surgically, including various minimally invasive therapies, or medically. Medical treatment can consist of endocrine treatment by inhibiting the enzyme 5α-reductase to reduce the formation of dihydrotestosterone and/or α1-adrenergic receptor (α1-AR) antagonists. All surgical approaches to LUTS/BPH treatment, including the minimally invasive ones, and also all endocrine approaches reduce prostate size and hence are primarily targeted against the static component. In contrast, α1-AR antagonists oppose prostatic smooth muscle contraction and are thus targeted against the dynamic component of obstruction. More recent concepts highlight the possibility that the beneficial effects of α1-AR antagonists may depend not only upon prostatic smooth muscle relaxation but may also involve other mechanisms related to α1-AR in the urinary bladder and/or spinal cord. Three distinct α1-AR subtypes exist, which are designated α1A, α1B and α1D. Prostate contraction occurs predominantly if not exclusively via α1A-ARs, whereas the human urinary bladder and spinal cord mainly express α1D-ARs. Several α1-AR antagonists are available for the treatment of LUTS/BPH, and alfuzosin, doxazosin, tamsulosin and terazosin are most frequently used internationally; as a class they have become the most often used rational treatment modality for LUTS/BPH. While all four drugs are similarly effective, tamsulosin ((-)-5-[2-[[2-((O-ethoxyphenoxy)ethyl]amino] propyl]-2-methoxybenzenesulfonamide, formerly known as YM 12617 or YM 617) differs from the other drugs chemically because it is a methoxybenzene
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sulphonamide derivative rather than a quinazoline. Moreover, tamsulosin has greater affinity for $\alpha_{1A}$-AR, and to a lesser extent to $\alpha_{1D}$-AR, than for $\alpha_{1B}$-AR whereas the quinazolines lack such subtype selectivity. How these chemical differences relate to potential differences in tolerability between the drugs, remains to be determined. This manuscript will focus on tamsulosin. Since its introduction in the 1990’s, tamsulosin has been available in a modified release (MR) formulation, and more recently an oral controlled absorption system (OCAS) formulation has been introduced. In this paper, we will summarize the pharmacokinetics and clinical data of both the MR and the OCAS formulation of tamsulosin. Special emphasis will be on the latter, since the former has been reviewed comprehensively several times in the past.

**PHARMACOKINETICS AND METABOLISM**

**Tamsulosin modified release formulation**

Because an immediate-release formulation of tamsulosin exhibits rapid absorption and increase in plasma concentration upon oral administration, possibly leading to cardiovascular side effects, a MR capsule formulation was developed. This formulation utilises a multi-unit layer coated pellet technology. The pellets have a drug core, and the MR characteristics are provided by the layer surrounding the pellets. These are hydrated in the gastrointestinal tract, where the drug is released.

The pharmacokinetics of tamsulosin MR have been assessed in several studies in young and elderly subjects. Absorption of tamsulosin from the MR formulation after oral administration is gradual, with a bioavailability of about 100% under fasting conditions. The pharmacokinetics are dose linear following single and multiple doses. The time to maximum concentration ($t_{max}$) is 4-5 hours under fasting conditions and 6-7 hours when administered with food. Fasting conditions increase the bioavailability by 30% and the mean maximum plasma concentration ($C_{max}$) by 40-70% compared to fed conditions. All clinical studies were based upon the recommendation that tamsulosin MR capsules should be taken after a meal, as also specified in the US package insert or the European Summary of Product Characteristics.

The mean steady state apparent volume of distribution of tamsulosin was 16 L/kg after intravenous infusion to 10 volunteers of 0.125 mg tamsulosin MR over 4 hours. In vitro, the plasma protein binding (mainly to $\alpha_i$-acid glycoprotein) was approximately 99%. The half-life of tamsulosin MR is approximately 9-13 hours in young healthy volunteers compared to 14-15 hours in elderly subjects, and the area under the curve is 40% higher in subjects aged 55-75 compared to subjects aged 20 to 32 years. A summary of the pharmacokinetic properties of tamsulosin MR is given in table 1.

Tamsulosin is metabolised in the liver by the cytochrome P450 isoymes, primarily CYP3A4 and CYP2D6, although minor contributions from other CYPs cannot be excluded.
biologically active R-(-)-isomer of tamsulosin does not undergo bioconversion to the inactive S-(+)-isomer. The tamsulosin metabolites are considered to possess similar or less potent pharmacological activities compared to tamsulosin, based on antagonising effects on radioligand binding to rat liver and kidney 1-adrenoceptors. However, the total concentration of tamsulosin metabolites accounted for only a small percentage of the unchanged drug at the maximum plasma tamsulosin concentrations in human volunteers.

Studies in patients with normal renal function and patients with moderate to severe renal impairment showed an increase of the area under the curve of total tamsulosin with increasing renal impairment. However, free tamsulosin levels were much less affected by renal impairment, and no statistically significant differences were noted between the groups of subjects. Since unbound tamsulosin is primarily responsible for the pharmacodynamic effect, dose adjustments of tamsulosin do not seem necessary in renal failure.

A study comparing the pharmacokinetics of tamsulosin in 8 subjects with hepatic insufficiency (Child-Pugh classification grade A or B) compared to 8 subjects with a normal hepatic function, showed decreased 1-adrenergic receptor interaction, leading to a significant increase of unbound plasma tamsulosin. This, however, led to an increase in renal clearance and as a result, hepatic impairment did not affect the pharmacokinetics of tamsulosin in a clinically relevant manner. Therefore, it appears that no adjustment of tamsulosin dose is required in the presence of mild-to-moderate hepatic impairment.

To the best of our knowledge, the pharmacokinetics of tamsulosin have not been tested in patients with severe hepatic impairment.

### Tamsulosin oral controlled absorption system formulation

A new tamsulosin tablet formulation based upon the proprietary OCAS technology was recently developed. The release of the active ingredient from the tamsulosin MR capsule is dependent on the presence of water in the gastrointestinal tract, and hence drug release is impeded during the passage through the colon, where the amount of water is very limited. In contrast, the tamsulosin OCAS tablet consists of a gel matrix comprised of a gel-forming and a gel-enhancing agent. This tablet is hydrated very
rapidly, and complete hydration occurs prior to its arrival in the colon. The hydrated gel matrix has sufficient strength to achieve drug release in the colon despite poor local water availability.\textsuperscript{15}

The single dose pharmacokinetics of three tamsulosin OCAS 0.4 mg formulations (S2, S3, S4, differing in the total amount of gel-enhancing agent) and tamsulosin MR 0.4 capsules were compared in young, healthy volunteers.\textsuperscript{15} The pharmacokinetics of all 3 OCAS formulations differed from the MR formulation in several ways. Firstly, $C_{\text{max}}$ values were reduced, yielding smaller peak-to-trough ratios and more constant 24 h plasma concentrations. Secondly, the total drug exposure as assessed by the area under the curve was lower. Thirdly, the pharmacokinetics of tamsulosin OCAS were not affected by concomitant food intake. On the other hand, the OCAS formulation had only minor effects on $t_{\text{max}}$ or the terminal elimination half-life. Among the three tested OCAS formulations, S3 was selected for further development. This pharmacokinetic profile was confirmed in subsequent studies.\textsuperscript{24-26} A summary of the pharmacokinetic properties of tamsulosin OCAS is given in table 1. There is no evidence to suggest that the distribution, metabolism or excretion of tamsulosin OCAS differs from that of tamsulosin MR as described above.

**CLINICAL EFFICACY**

**Tamsulosin modified release formulation**

The dose-dependency of the clinical effects of tamsulosin MR was investigated in a European phase II study comparing doses of 0.2, 0.4 and 0.6 mg q.d.\textsuperscript{27} as well as two US phase III studies comparing 0.4 and 0.8 mg q.d..\textsuperscript{28, 29} These studies demonstrate that the dose of 0.4 mg q.d. is maximally effective for the vast majority of patients. Hence, this is the only registered dose in European countries. In the US, a dose-escalation to 0.8 mg q.d. is possible, whereas in Japan and some other Asian countries, 0.2 mg q.d. is the recommended dose.

The overall efficacy and safety of tamsulosin MR relative to placebo was evaluated in two European randomized, double-blind phase III studies, which have been reported as a meta-analysis of both\textsuperscript{30}, and two US phase III studies.\textsuperscript{28, 29} The European studies lasted 12 weeks and investigated the 0.4 mg dose only, whereas the US studies lasted 13 weeks and investigated both 0.4 and 0.8 mg tamsulosin MR.

In the European studies, maximum urinary flow ($Q_{\text{max}}$) improved significantly more with tamsulosin (+1.6 ml/s) than with placebo (+0.6 ml/s; $p = 0.002$).\textsuperscript{30} The total Boyarsky symptom score significantly improved compared to baseline in both the tamsulosin as the placebo treated patients at each subsequent study visit. However, at each time point, the extent of the improvements was significantly greater in the tamsulosin group than in the placebo group. At endpoint for example, the decrease in total Boyarsky
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Tamsulosin – MR and OCAS

Symptom score was 2.4 points (-25.5%) in the placebo group compared with 3.3 (-35.1%) in the tamsulosin group (p=0.002). In addition, significantly more tamsulosin (66%) than placebo treated patients (49%) had a ≥25% decrease in total symptom score at endpoint. The lifestyle questionnaire showed that the ‘sexual functioning’ and ‘worries and concerns’ scores at completion of the studies significantly improved in the patients treated with tamsulosin compared to placebo.30,31 Both US studies also found statistically significant reductions in total American Urological Association (AUA) symptom score (also known as the International Prostate Symptom Score (IPSS)) and Qmax in the tamsulosin group compared with placebo. However, the differences in AUA symptom score and Qmax between the 2 doses were not statistically significant, thereby implying that an increase from 0.4 to 0.8 mg/day by forced titrations does not result in further therapeutic benefits.28,29 These studies also addressed the speed of response to treatment. The AUA symptom score was shown to improve as early as the first week of treatment and changes of Qmax were apparent within 4-8 hours after the first tamsulosin dose.

Open-label extension trials of up to 6 years were conducted in both the European and the US placebo-controlled studies.32-35 The overall conclusion from these extension trials was that the improvements in symptom scores and urinary flow rates were sustained throughout the additional observational period in patients who had remained in the studies.

Large post-marketing surveillance studies have investigated possible differences in treatment effect in subgroups of patients. Two studies assessing a total of 19,365 patients found that tamsulosin MR was similarly effective in all age groups and that its efficacy in patients with severe symptoms was at least as large as in those with mild to moderate symptoms.36,37 A separate 12-week post-marketing surveillance study reported a similar efficacy upon morning and evening dosing.38 Several studies have directly compared the efficacy of tamsulosin MR to that of other a1-AR antagonists. In line with the indirect comparisons between drugs7,8, these studies have typically reported similar efficacy of both drugs. Such comparisons were reported for tamsulosin 0.2 mg q.d. relative to terazosin 1-5 mg q.d. in a Korean population39 and to terazosin 2 mg in Chinese patients.40 In Caucasian patients such comparisons were reported for tamsulosin 0.4 mg q.d. relative to alfuzosin 2.5 mg t.i.d.41, alfuzosin 10 mg q.d.42 or terazosin 5 mg q.d.43 One study comparing 0.4-0.8 mg tamsulosin MR to 4-8 mg doxazosin reported a greater efficacy for the latter44 but is difficult to interpret due to a very small patient group being studied. Taken together, these studies demonstrate that all a1-AR antagonists have similar efficacy in improving symptoms and flow of LUTS/BPH patients.
Tamsulosin oral controlled absorption system formulation

Based upon the smoothened pharmacokinetic profile of tamsulosin OCAS it had been hoped that escalation to higher and hence more effective but nevertheless well-tolerated doses might be possible. Therefore, a phase 2b dose-finding study has randomly assigned a total of 839 patients to 0.4, 0.8, 1.2 mg tamsulosin OCAS q.d. or placebo for 12 weeks.\textsuperscript{45} The mean IPSS reduction at the endpoint was 6.0 with placebo and 7.6, 8.1 and 8.2 with tamsulosin OCAS 0.4, 0.8 and 1.2 mg, respectively (all p<0.05 vs. placebo). The differences between the three doses were judged to be clinically irrelevant. The mean improvements in the Quality of Life (QoL) item of the IPSS from baseline to endpoint in the different treatment groups were also statistically significantly different from placebo but similar among the three tamsulosin OCAS doses. The incidence of treatment-related adverse events was higher with the 0.8 mg and in particular with the 1.2 mg doses than with the 0.4 mg dose or placebo. Therefore, it was decided to only investigate the tamsulosin OCAS 0.4 and 0.8 mg doses in a subsequent trial.

In a phase 3a randomized, double-blind trial, a total of 2152 patients received placebo, tamsulosin OCAS 0.4 mg, tamsulosin 0.8 mg OCAS or tamsulosin MR 0.4 mg for 12 weeks \textsuperscript{46}. Reductions of IPSS, responder rates (defined as patients with a minimally 25\% reduction of total IPSS) and improvements in the QoL score were greater with all three active treatments than with placebo, but no clinically relevant differences were seen among active treatments. For example, IPSS reductions were 5.8, 8.0, 7.7, and 8.0 points with placebo, tamsulosin MR 0.4 mg, tamsulosin OCAS 0.4 mg and tamsulosin OCAS 0.8 mg, respectively (Figure 1). Since the incidence of adverse events of tamsulosin OCAS 0.8 mg was numerically higher than that of tamsulosin OCAS 0.4 mg (see below), the latter was concluded to be the recommended dose.

A randomised placebo-controlled pilot study was conducted to assess the effect of tamsulosin OCAS 0.4 mg on nocturia, the hours of undisturbed sleep and QoL in 117 patients with LUTS/BPH and at least 2 nocturia episodes per night.\textsuperscript{24} Neither the mean

\begin{figure}[h]
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\includegraphics[width=\textwidth]{Figure1.png}
\caption{Time course of symptom improvement (as measured by the IPSS) in LUTS/BPH patients treated with the MR or OCAS formulation of tamsulosin. Reproduced with permission from \textsuperscript{46}.}
\end{figure}
increase in hours of undisturbed sleep nor the mean decrease in number of nocturnal voids from baseline showed a statistically significant difference between tamsulosin OCAS and placebo, whereas the mean reduction in IPSS nocturia score did statistically significantly improve with tamsulosin OCAS compared to placebo. Interestingly, a significant effect on nocturia (based upon the corresponding question of the IPSS) had previously also been demonstrated for tamsulosin MR.47

SAFETY AND TOLERABILITY

Tamsulosin modified release formulation

The safety and tolerability of tamsulosin MR has been assessed in one phase II27, two European phase III30, two US phase III28, 29 and several other randomised controlled trials. Moreover, open-label, post-marketing surveillance studies have assessed the relative tolerability of tamsulosin MR in subgroups of patients such as those with specific comorbidities or various concomitant medications. Finally, clinical pharmacology studies in small numbers of subjects were performed to gain mechanistic insight into the tolerability of tamsulosin. All these studies looked into adverse events in general and at blood pressure lowering and abnormal ejaculation in particular.

The phase II and III clinical trials showed a comparable overall incidence of adverse events between the tamsulosin MR 0.4 mg and placebo groups. The open label extensions of these trials, as well as the post-marketing surveillance studies, confirmed the good overall tolerability of tamsulosin. In addition, it was shown that tamsulosin maintains its good global tolerability in patients with concomitant disease or co-medication. In direct comparative studies with other α1-AR antagonists, the overall incidence of adverse events was similar with tamsulosin 0.4 mg/day compared to alfuzosin 2.5 mg t.i.d., extended release alfuzosin 10-15 mg q.d., terazosin 5 mg q.d. following titration and in a small study with tamsulosin 0.4-0.8 mg as compared to doxazosin 4-8 mg. In contrast, comparison of 0.2 mg tamsulosin to terazosin 1-5 mg in a Korean population and to terazosin 2 mg in Chinese patients, showed a lower overall incidence of adverse events in the tamsulosin groups.

Since α1-AR antagonists were originally introduced for the treatment of hypertension, adverse events related to blood pressure lowering have been addressed specifically in clinical trials. In both the European and the US placebo-controlled trials, tamsulosin did not lower systolic or diastolic blood pressure relative to placebo in a clinically relevant manner. The incidence of symptomatic orthostatic hypotension in tamsulosin MR 0.4 mg treated patients did not statistically differ to placebo. A small but statistically significant difference in incidence of orthostatic hypotension with the tamsulosin 0.8 mg dose was found in one but not in another US trial. Based upon an aggregate of randomized controlled, observational and clinical pharmacology studies, it appears
that cardiovascular comorbidity or concomitant use of antihypertensive drugs do not adversely affect the cardiovascular tolerability of tamsulosin. A clinical pharmacology study suggests that tamsulosin MR when taken on an empty stomach has greater cardiovascular effects than after the recommended use after a meal.

In direct comparative studies, terazosin was shown to cause more symptomatic orthostatic hypotension than tamsulosin, and both terazosin and alfuzosin 2.5 mg t.i.d. were shown to be associated with a significantly greater reduction in blood pressure than tamsulosin. A direct comparison of tamsulosin MR with alfuzosin extended release 10 and 15 mg detected orthostatic hypotension in 1.9%, 2.6% and 3.8% of patients, respectively.

Abnormal ejaculation occurred significantly more frequently with tamsulosin than with placebo in both the European and the US placebo-controlled studies. The incidence of abnormal ejaculation was dose-related; 6-11% of the patient receiving tamsulosin MR 0.4 mg and 18% of the patients receiving tamsulosin MR 0.8 mg reported abnormal ejaculation, compared to almost 0% of the placebo-treated patients. Younger patients appear more susceptible to this adverse event than older patients. Indirect comparisons of placebo controlled trials show a greater incidence of abnormal ejaculation with tamsulosin as compared to other α1-AR antagonists. However, in direct comparative studies, the numerically higher incidence of abnormal ejaculation in tamsulosin treated patients compared to the other α1-AR antagonists failed to reach statistical significance, unless very large patient numbers were compared.

Tamsulosin oral controlled absorption system formulation

In the above-mentioned phase 2b dose-finding study, the percentage of patients reporting at least one treatment emerging adverse event was comparable for tamsulosin OCAS 0.4 and 0.8 mg and placebo (26-30% of the patients). The incidence was slightly higher with the 1.2 mg dose (36%). The incidence of dizziness was comparable for tamsulosin OCAS 0.4 mg (0.5%) and placebo (1.4%), whereas it was higher with both the 0.8 mg and the 1.2 mg doses of tamsulosin OCAS. Two patients reporting treatment-related dizziness discontinued from the study (one on 0.8 mg and one on 1.2 mg tamsulosin OCAS). There were no changes of any clinical concern in standing systolic and diastolic blood pressure in any of the treatment groups. Abnormal ejaculation did not occur frequently with placebo (0.9%) or with the 0.4 mg dose (2.0%). However, it increased with the 0.8 mg dose (4.4%) and even more so with the 1.2 mg dose (8.1%). None of the patients reporting abnormal ejaculation discontinued from the study due to this treatment emerging adverse event.

In the phase 3a study assessing 2152 patients, dizziness and abnormal ejaculation were the most frequently reported adverse events. The incidence of dizziness was comparable for the 0.4 mg OCAS dose (1.4%) and placebo (1.4%) and slightly but not significantly higher with tamsulosin 0.4 mg MR (1.7%) and tamsulosin OCAS 0.8 mg (2.4%). The incidence of abnormal ejaculation was significantly higher with tamsulosin MR 0.4 mg
(3.1%) and tamsulosin OCAS 0.8 mg (5.3%), but not with tamsulosin OCAS 0.4 mg (1.9%), as compared to placebo (0.3%). Minor reductions in blood pressure relative to baseline were shown in all treatment groups, including the placebo group; tamsulosin OCAS 0.4 mg, however, was associated with the smallest reduction in blood pressure.

In a study with 18 healthy male volunteers, tamsulosin OCAS 0.4 mg tablets showed less cardiovascular α₁-AR antagonism, i.e. less inhibition of vasoconstriction and total peripheral resistance, than tamsulosin MR 0.4 mg capsules after a single dose in the fasted state. These data indicate that on an empty stomach, tamsulosin OCAS may provide a better cardiovascular safety profile than tamsulosin MR. To compare the cardiovascular safety of tamsulosin OCAS 0.4 mg and tamsulosin MR 0.4 mg, a double-blind two-period crossover study was conducted, in which 40 healthy elderly males were randomised to one of two treatment sequences. For the cardiovascular safety assessments, orthostatic stress tests were performed and vital signs were measured in the fasting state. An increase of the incidence of positive orthostatic stress tests was encountered in both tamsulosin OCAS 0.4 mg (17.5%) and in tamsulosin MR 0.4 mg (31.7%) treated patients compared to pre-dose (2.5%). However, tamsulosin OCAS caused significantly less orthostasis than tamsulosin MR based upon an analysis of the discordant pairs (that is a positive test result for only one of the two treatments). The analysis of the vital signs confirmed that the OCAS formulation caused smaller blood pressure reductions and increase in pulse rate compared to the MR formulation. Both of the above studies indicate an improved cardiovascular tolerability of tamsulosin OCAS as compared to tamsulosin MR under fasting conditions. In the interpretation of these differences it should be noted that dosing of tamsulosin MR under fasting conditions is not recommended. Indeed, in similar studies it had been shown that lack of food intake decreases the cardiovascular tolerability of tamsulosin MR. Whether a similar difference exists between tamsulosin OCAS and tamsulosin MR when both are taken after a meal, remains unknown. However, it can safely be assumed that a certain fraction of elderly males using tamsulosin MR may not always take their medication after a meal despite official recommendations to the contrary. Therefore, the above differences between tamsulosin OCAS and tamsulosin MR may have some practical value despite study conditions which were biased in favour of tamsulosin OCAS.

**REGULATORY AFFAIRS**

Tamsulosin MR has been introduced in many countries including all major markets for the treatment of LUTS/BPH. Tamsulosin OCAS has been approved by the European Medicines Evaluation Agency and the Canadian authorities; it has been introduced in some European countries, and other European countries and Canada are expected to follow in 2006.
CONCLUSIONS

Tamsulosin is an a_1-AR antagonist for the treatment of LUTS/BPH, and has become the world-wide market leader. Since its introduction, tamsulosin has been available in a MR formulation, and recently, an OCAS formulation has been introduced. The efficacy of tamsulosin MR is equivalent to the efficacy of other a_1-AR antagonists and is maintained for many years. The overall tolerability of tamsulosin 0.4 mg MR is comparable to placebo and is not affected by cardiovascular comorbidity or concomitant medication. Furthermore, tamsulosin has a better cardiovascular safety profile than several other a_1-AR antagonists. The tamsulosin 0.4 mg OCAS tablet has been shown to have smoothened controlled release pharmacokinetics compared with the 0.4 mg MR capsule. While the efficacy of tamsulosin OCAS and tamsulosin MR are similar, the OCAS formulation appears to have minor advantages with regard to tolerability, which may become clinically relevant if the MR capsule is taken on an empty stomach.

OUTLOOK

A recently published large long-term study has demonstrated that the 5a-reductase inhibitor finasteride and the a_1-AR antagonist doxazosin reduce the symptomatic long-term progression of LUTS/BPH.\textsuperscript{52} However, both types of drugs do so by different mechanisms, i.e. the 5a-reductase inhibitor mainly by reducing prostate growth and preventing acute urinary retention and the a_1-AR antagonist mainly by preventing symptom score progression. Therefore, it is not surprising that a combination of both drugs proved superior with regard to overall clinical progression than either active treatment alone. However, such combination treatment also has medical costs, i.e. leads to additive side effects. Since combination treatment is intended for long-term use, managing such side effect potential is important. When it is assumed that the effects of finasteride and doxazosin in the above-mentioned study represent class effects, it appears rational to choose an a_1-AR antagonist with a very low side effect potential such as tamsulosin. Whether a 5a-reductase inhibitor/tamsulosin combination is indeed beneficial in long-term treatment of LUTS/BPH, is currently undergoing clinical investigation.

HIGHLIGHTS

Tamsulosin is an a_1-AR antagonist with some selectivity for a_{1A}-AR. Tamsulosin is effective and well tolerated in the treatment of LUTS/BPH, and such effects are maintained for at least 6 years.
An MR and an OCAS formulation of tamsulosin are available for q.d. dosing, the latter having a smoothened pharmacokinetic profile, which is independent of concomitant food intake.

The MR and OCAS formulation of tamsulosin are equally effective.

The MR and OCAS formulation are similarly well tolerated, but the OCAS formulation may offer advantages when the drug is taken on an empty stomach.

The tolerability of tamsulosin is maintained in the presence of cardiovascular comorbidity and concomitant blood pressure-lowering medication.
REFERENCES


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38. Michel MC, Neumann HG, Mehlinger L, Schumacher H, Goepel M. Does the time of administration (morning or evening) affect the tolerability or efficacy of tamsulosin? BJU Int 2001;87:31-4.


42. Nordling J. Efficacy and safety of two doses (10 and 15 mg) of alfuzosin or tamsulosin (0.4 mg) once daily for treating symptomatic benign prostatic hyperplasia. BJU Int 2005;95:1006-12.


50. van Dijk MM, de la Rosette JJ, Michel MC. Effects of a1-adrenergic receptor antagonists on male sexual function. Drugs 2006;In press.
