



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

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Tamsulosin is an  $\alpha_1$ -adrenergic receptor antagonist. For many years, it has been available in a modified-release (MR) capsule formulation only, but recently, an oral-controlled absorption system (OCAS) tablet formulation has been introduced. Tamsulosin is an effective treatment for patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia 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. The tamsulosin 0.4 mg OCAS tablet has a smoothened pharmacokinetic profile compared with the 0.4 mg MR capsule. While the efficacy of tamsulosin OCAS and tamsulosin MR are comparable, the OCAS formulation appears to have minor advantages regarding tolerability, which may become clinically relevant if the MR capsule is taken on an empty stomach.

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 [1]. Clinically relevant LUTS/BPH occur less frequently than the histological diagnosis but nevertheless are present in about 30% of elderly males [2]. 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 5 $\alpha$ -reductase to reduce the formation of dihydrotestosterone and/or  $\alpha_1$ -adrenergic receptor ( $\alpha_1$ -AR)

antagonists. All surgical approaches to LUTS/BPH treatment, including those that are minimally invasive, and also all endocrine approaches reduce prostate size and hence are primarily targeted against the static component. In contrast,  $\alpha_1$ -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  $\alpha_1$ -AR antagonists may depend not only upon prostatic smooth muscle relaxation but may also involve other mechanisms related to  $\alpha_1$ -AR in the urinary bladder and/or spinal cord [3]. Three distinct  $\alpha_1$ -AR subtypes exist, which are designated  $\alpha_{1A}$ ,  $\alpha_{1B}$  and  $\alpha_{1D}$  [4]. Prostate contraction occurs predominantly if not exclusively via  $\alpha_{1A}$ -ARs, whereas the human urinary bladder and spinal cord mainly express  $\alpha_{1D}$ -ARs [5].

Several  $\alpha_1$ -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 [6]. While all four drugs are similarly effective [7,8], 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 sulfonamide 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 [9–11]. How these

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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 [12,13].

### Pharmacokinetics & metabolism

#### *Tamsulosin modified-release formulation*

Since an immediate-release formulation of tamsulosin exhibits rapid absorption and a rapid increase in plasma concentration upon oral administration, possibly leading to cardiovascular side effects, a MR capsule formulation was developed [12,14]. This formulation utilises a multiunit 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 [15].

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 [16]. The pharmacokinetics are dose linear following single and multiple doses [101]. The time to maximum concentration ( $t_{\max}$ ) is 4–5 h under fasting conditions and 6–7 h when administered with food [101]. Fasting conditions increase the bioavailability by 30% and the mean maximum plasma concentration ( $C_{\max}$ ) by 40–70% compared with fed conditions [101]. 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 ten volunteers of 0.125 mg tamsulosin MR over 4 h [16,101]. *In vitro*, the plasma protein binding (mainly to  $\alpha_1$ -acid glycoprotein) was approximately 99% [14]. The half-life of tamsulosin MR is approximately 9–13 h in young healthy volunteers compared to 14–15 h in elderly subjects, and the area under the curve is 40% higher in subjects aged 55–75 years compared with those aged 20–32 years [101]. A summary of the pharmacokinetic properties of tamsulosin MR is given in Table 1.

Tamsulosin is metabolized in the liver by the cytochrome P (CYP)450 isozymes, primarily CYP3A4 and CYP2D6, although minor contributions from other CYPs cannot be excluded [17]. The biologically active *R*-(-)-isomer of tamsulosin does not undergo bioconversion to the inactive *S*-(+)-isomer [101]. 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  $\alpha_1$ -adrenoceptors [18]. 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 [17,19].

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 [20,21]. 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

**Table 1. Pharmacokinetic properties of 0.4 mg of the MR and OCAS formulation of tamsulosin as administered under fed conditions.**

|                               | Tamsulosin MR | Tamsulosin OCAS |
|-------------------------------|---------------|-----------------|
| $t_{\max}$ (h)                | 6–7           | 8–9             |
| $C_{\max}$ (ng/ml)            | 14            | 16              |
| $t_{1/2}$ (h)                 | 14–15         | 14–15           |
| Clearance (l/h)               | 2.88          | 2.88            |
| Volume of distribution (l/kg) | 16            | 16              |
| Plasma protein binding (%)    | 99            | 99              |

MR: Modified release; OCAS: Oral-controlled absorption system.

responsible for the pharmacodynamic effect, dose adjustments of tamsulosin do not seem necessary in renal failure [20–22].

A study comparing the pharmacokinetics of tamsulosin in eight subjects with hepatic insufficiency (Child-Pugh classification grade A or B) compared with eight subjects with a normal hepatic function, showed decreased  $\alpha_1$ -acid glycoprotein binding levels resulting in a significant increase of unbound plasma tamsulosin [20]. 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 [20,22]; 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 [15]. 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 [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 mg capsules were compared in young, healthy volunteers [15]. The pharmacokinetics of all three OCAS formulations differed from the MR formulation in several ways. First,  $C_{\max}$  values were reduced, yielding smaller peak-to-trough ratios and more constant 24 h plasma concentrations. Second, 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  $t_{\max}$  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 [23–25]. 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 once-daily [26] as well as two US Phase III studies comparing 0.4 and 0.8 mg once-daily [27,28]. These studies demonstrate that the dose of 0.4 mg once-daily is maximally effective for the vast majority of patients. Hence, this is the only registered dose in European countries. In the USA, a dose-escalation to 0.8 mg once-daily is possible, whereas in Japan and some other Asian countries, 0.2 mg once-daily 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 [29], and two US Phase III studies [27,28]. The European studies lasted 12 weeks and investigated the 0.4-mg dose only, whereas the US studies lasted 13 weeks and investigated both the 0.4 and 0.8 mg tamsulosin MR.

In the European studies, maximum urinary flow ( $Q_{\max}$ ) improved significantly more with tamsulosin (+1.6 ml/s) than with placebo (+0.6 ml/s;  $p = 0.002$ ) [29]. The total Boyarsky symptom score significantly improved compared with baseline in both the tamsulosin- and 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 end point, for example, the decrease in total Boyarsky 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 decrease in total symptom score equivalent to or greater than 25% at end point. 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 with placebo [29,30].

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  $Q_{\max}$  in the tamsulosin group compared with placebo. However, the differences in AUA symptom score and  $Q_{\max}$  between the two doses were not statistically significant, thereby implying that an increase from 0.4–0.8 mg once-daily by forced titrations does not result in further therapeutic benefits [27,28]. 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  $Q_{\max}$  were apparent within 4–8 h after the first tamsulosin dose.

Open-label extension trials of up to 6 years were conducted in both the European and US placebo-controlled studies [31–34]. 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 postmarketing 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 as least as large as in those with mild-to-moderate symptoms [35,36]. A separate 12-week postmarketing surveillance study reported a similar efficacy upon morning and evening dosing [37].

Several studies have directly compared the efficacy of tamsulosin MR with that of other  $\alpha_1$ -AR antagonists. In line with the indirect comparisons between drugs [7,8], these studies have typically reported similar efficacy of both drugs. Such comparisons were reported for tamsulosin 0.2 mg once-daily relative to terazosin 1–5 mg once-daily in a Korean population [38] and to terazosin 2 mg in Chinese patients [39]. In Caucasian patients such comparisons were reported for tamsulosin 0.4 mg once-daily relative to alfuzosin 2.5 mg three times a day [40], alfuzosin 10 mg once-daily [41] or terazosin 5 mg once-daily [42]. One study comparing 0.4–0.8 mg tamsulosin MR to 4–8 mg doxazosin reported a greater efficacy for the latter [43] but is difficult to interpret due to the very small patient group studied. Taken together, these studies demonstrate that all  $\alpha_1$ -AR antagonists have similar efficacy in improving symptoms and flow of LUTS/BPH patients.

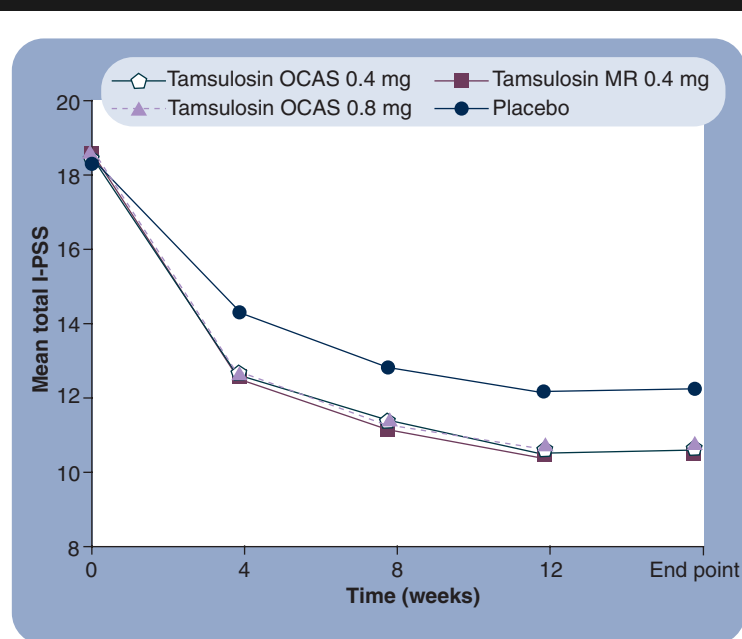
### ***Tamsulosin oral-controlled absorption system formulation***

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 IIb dose-finding study has randomly assigned a total of 839 patients to 0.4, 0.8, 1.2 mg tamsulosin OCAS once-daily or placebo for 12 weeks [44]. The mean IPSS reduction at end point 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 end point 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 IIIa 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 [45]. 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 observed 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 randomized, 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 two nocturia episodes/night [23]. Neither the mean increase in hours of undisturbed sleep nor the mean decrease in number of nocturnal voids from baseline showed a statistically significant

**Figure 1. Time course of symptom improvement (as measured by the IPSS) in LUTS/BPH patients treated with the MR or OCAS formulation of tamsulosin.**



BPH: Benign prostatic hyperplasia; IPSS: International Prostate Symptom Score; LUTS: Lower urinary tract symptom; MR: Modified release; OCAS: Oral-controlled absorption system.  
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difference between tamsulosin OCAS and placebo, whereas the mean reduction in IPSS nocturia score did statistically significantly improve with tamsulosin OCAS compared with placebo. Interestingly, a somewhat smaller but significant effect on nocturia (based upon the corresponding question of the Boyarski symptom score) had previously also been demonstrated for tamsulosin MR [46].

### Safety & tolerability

#### *Tamsulosin modified-release formulation*

The safety and tolerability of tamsulosin MR has been assessed in one Phase II [26], two European Phase III [29], two US Phase III [27,28] and several other randomized controlled trials. Moreover, open-label, postmarketing 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 of these studies examined adverse events in general and blood pressure (BP)-lowering and abnormal ejaculation in particular.

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 postmarketing surveillance studies, confirmed the good overall tolerability of tamsulosin [31–36]. In addition, it was shown that tamsulosin maintains its good global tolerability in patients with concomitant disease or comedication [35]. In direct comparative studies with other  $\alpha_1$ -AR antagonists, the overall incidence of adverse events was similar with tamsulosin 0.4 mg once-daily compared with alfuzosin 2.5 mg three times daily [40], extended-release alfuzosin 10–15 mg once-daily [41], terazosin 5 mg once-daily following titration [42] and in a small study with tamsulosin 0.4–0.8 mg compared with doxazosin 4–8 mg [43]. In contrast, a comparison of 0.2 mg tamsulosin with terazosin 1–5 mg in a Korean population [38] and terazosin 2 mg in Chinese patients [39], showed a lower overall incidence of adverse events in the tamsulosin groups.

Since  $\alpha_1$ -AR antagonists were originally introduced for the treatment of hypertension, adverse events related to BP-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 BP relative to placebo in a clinically relevant manner [27–29]. The incidence of symptomatic orthostatic hypotension in tamsulosin MR 0.4 mg-treated patients did not statistically differ to placebo [27–29]. A small but statistically significant difference in incidence of orthostatic hypotension with the tamsulosin 0.8-mg dose was found in one [28] but not in another US trial [27]. 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 [47]. 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 [24].

In direct comparative studies, terazosin was shown to cause more symptomatic orthostatic hypotension than tamsulosin [48], and both terazosin and alfuzosin 2.5 mg three times daily were shown to be associated with a significantly greater reduction in BP than tamsulosin [38–40,48]. 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 [41].

Abnormal ejaculation occurred significantly more frequently with tamsulosin than with placebo in both the European and the US placebo-controlled studies [27–29]. 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 with almost 0% of the placebo-treated patients [27,28]. 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 compared with other  $\alpha_1$ -AR antagonists [49]. However, in direct comparative studies, the numerically higher incidence of abnormal ejaculation in tamsulosin-treated patients compared with other  $\alpha_1$ -AR antagonists failed to reach statistical significance, unless very large patient numbers were compared [40–42].

Very recently, a novel adverse event has been reported in patients undergoing cataract surgery termed ‘intraoperative floppy iris syndrome’ (IFIS) [50]. IFIS is characterized by excessive billowing and fluttering of the iris during phacoemulsification. The occurrence of IFIS in tamsulosin treated patients has been confirmed by other investigators [51]. IFIS was observed under conditions where mydriasis had been induced by local administration of a drug cocktail including the  $\alpha_1$ -AR agonist phenylephrine. While antagonism of the mydriatic effects of phenylephrine was not unexpected for  $\alpha_1$ -AR antagonists, it was reported, based upon very limited data, that IFIS had not been observed with  $\alpha_1$ -AR antagonists other than tamsulosin [52] although it would have been predicted to be a class effect based upon the above data. Indeed, recent studies in rabbits demonstrate that iridal effects of tamsulosin are shared by various other  $\alpha_1$ -AR antagonists [52]. Moreover, it has been reported in patients that intracameral administration of phenylephrine prevented the occurrence of IFIS in tamsulosin-treated patients undergoing cataract surgery [53], indicating that it is a fully reversible condition which can easily be managed if adequate measures are taken. Recent regulatory information from the US FDA suggests that patients considered for cataract surgery should specifically be questioned as to whether they have taken tamsulosin or other  $\alpha_1$ -AR antagonists; if so, ophthalmologists should be prepared for

possible modification to their surgical technique that may be warranted should IFIS be observed during the procedure.

#### ***Tamsulosin oral-controlled absorption system formulation***

In the above mentioned Phase IIb dose-finding study [44], 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- and 1.2-mg doses of tamsulosin OCAS. Two patients reporting treatment-related dizziness discontinued from the study (one on 0.8 and one on 1.2 mg tamsulosin OCAS). There were no changes of any clinical concern in standing systolic and diastolic BP 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 IIIa study assessing 2152 patients [45], 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%), compared with placebo (0.3%). Minor reductions in BP 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 BP.

In a study of 18 healthy male volunteers, tamsulosin OCAS 0.4 mg tablets showed less cardiovascular  $\alpha_1$ -AR antagonism, that is, less inhibition of vasoconstriction and total peripheral resistance, than tamsulosin MR 0.4 mg capsules after a single dose in the fasted state [25]. 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 randomized to one of two treatment sequences [54]. For the cardiovascular safety assessments, orthostatic stress tests were performed and vital signs were measured in the fasting state. An increase in the incidence of positive orthostatic stress tests was encountered in both tamsulosin OCAS 0.4 mg (17.5%) and 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 BP 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 [101]. Indeed, in similar studies it had been shown that lack of food intake decreases the cardiovascular tolerability of tamsulosin MR [24]. Whether a similar difference exists between tamsulosin OCAS and tamsulosin MR when both are taken after a meal, remains unknown. However, it can be safely 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. A comparison of tamsulosin OCAS 0.4 mg with alfuzosin XL extended release 10 mg under fed conditions in a similar study design also demonstrated fewer cardiovascular side effects for tamsulosin OCAS [55].

### 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.

### Expert commentary

Tamsulosin is an  $\alpha_1$ -AR antagonist for the treatment of LUTS/BPH, and has become the worldwide 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  $\alpha_1$ -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  $\alpha_1$ -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 5 $\alpha$ -reductase inhibitor finasteride and the  $\alpha_1$ -AR antagonist doxazosin reduce the symptomatic long-term progression of LUTS/BPH [56]. However, both types of drugs do so by different mechanisms, that is, the 5 $\alpha$ -reductase inhibitor mainly by reducing prostate growth and preventing acute urinary retention and the  $\alpha_1$ -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 as they lead 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  $\alpha_1$ -AR antagonist with a very low side effect potential such as tamsulosin. Whether a 5 $\alpha$ -reductase inhibitor/tamsulosin combination is indeed beneficial in long-term treatment of LUTS/BPH, is currently undergoing clinical investigation.

## Highlights

- Tamsulosin is an  $\alpha_1$ -adrenergic receptor (AR) antagonist with some selectivity for  $\alpha_{1A}$ -AR.
- Tamsulosin is effective and well tolerated in the treatment of lower urinary tract symptoms/benign prostatic hyperplasia, and such effects are maintained for at least 6 years.
- A modified-release (MR) and oral-controlled absorption system (OCAS) formulation of tamsulosin are available for once-daily dosing, the latter having a smoothened pharmacokinetic profile, which is independent of concomitant food intake.
- The MR and OCAS formulations 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.

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**Website**

101. Flomax (tamsulosin hydrochloride) package insert.  
[www.bidocs.com/renetnt/Prescribing+Information/PIs/Flomax+Caps/Flomax.pdf](http://www.bidocs.com/renetnt/Prescribing+Information/PIs/Flomax+Caps/Flomax.pdf)

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