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# Cardiovascular Safety of Tamsulosin Modified Release in the Fasted and Fed State in Elderly Healthy Subjects

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**Abstract**

***Objectives:*** The effect of food on the cardiovascular safety of tamsulosin modified release (MR) capsules 0.4 mg in elderly subjects was assessed both after single and multiple dosing.

***Methods:*** Thirty-six elderly (age $\geq$ 60 years) male volunteers were recruited and after a single-blind, placebo run-in period of 1 day were randomised to active treatment ($n$ = 24) or placebo ($n$ = 12). In each group the effect of food on vital signs and orthostatic stress testing was assessed in a crossover design after a single dose (Days 1 and 8 with a 7 day wash-out) and after 14 days of multiple dosing under fasting and fed conditions.

***Results:*** Changes in vital signs and orthostatic stress responses were more pronounced in the fasted than in the fed state. A total of 86 positive orthostatic stress tests were observed of which only three were symptomatic. Forty-six of these 86 tests were considered positive because of an effect on at least two criteria. The incidence of positive tests was higher in the fasted state and was increased by tamsulosin MR compared with placebo.

***Conclusions:*** Vital signs and orthostatic stress testing are more influenced by tamsulosin 0.4 mg MR capsules in the fasted than in the fed state. As tamsulosin MR is intended to be taken after breakfast or the first meal of the day, lack of compliance with this instruction may increase the incidence of cardiovascular adverse events in elderly males.


**Keywords:** Tamsulosin; Modified release capsule; Orthostatic hypotension; Benign prostatic hyperplasia; Lower urinary tract symptoms; Food effect

## 1. Introduction

During the last decade the usage of $\alpha_1$-adrenoceptor (AR) antagonists has become the mainstay treatment for lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH). $\alpha_1$-AR antagonists appear to exert their therapeutic benefit in patients with LUTS/BPH through relaxation of smooth muscle in the bladder outlet tract including the prostate and through additional mechanisms related to $\alpha_1$-ARs in the bladder and/or spinal cord [1–3]. The adverse events (AEs) most commonly associated with $\alpha_1$-AR antagonists, such as dizziness, headache, asthenia, tachycardia/palpitation, postural hypotension and syncope [4,5] are possibly related to the blood pressure lowering effect of these drugs. Consequently $\alpha_1$-AR subtype selectivity and/or preferential tissue distribution to the lower urinary tract are associated with differentiation between $\alpha_1$-AR antagonists in terms of cardiovascular tolerability [6,7].

Tamsulosin is an $\alpha_1$-AR antagonist structurally unrelated to the quinazoline family of $\alpha_1$-AR antagonists to which alfuzosin, doxazosin and terazosin belong. It has a relative selectivity for the $\alpha_{1A}$ and $\alpha_{1D}$ subtypes, which are predominantly located in the lower urinary tract, compared to the $\alpha_{1B}$ subtype that is more predominant in the cardiovascular system, especially in the elderly [7–12]. Since the introduction of tamsulosin as a modified release (MR) capsule in Japan (1993), Europe (1995) and the USA (1997), its efficacy and safety in the treatment of LUTS/BPH have been well documented [13–19]. The registered labelling of tamsulosin indicates that vasodilatory-related adverse events can occur and it recommends that tamsulosin is dosed after breakfast or the first meal of the day, in

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order to reduce the incidence of such events [20]. This is because tamsulosin is more rapidly and extensively absorbed in the fasted compared to the fed state and this results in a reduction in time to maximum plasma concentration and an increase in maximum plasma concentration and area under the curve (AUC) [20]. Such pharmacokinetic differences may increase the likeliness of adverse events in the fasted state.

This present study was designed to determine whether food effects of tamsulosin MR are associated with an altered cardiovascular tolerability. Our study was performed in elderly subjects since this group, which corresponds to the age group primarily using tamsulosin, is physiologically more prone to orthostatic hypotension than young people.

## 2. Materials and methods

### 2.1. Ethics

The study was conducted in accordance with the Declaration of Helsinki, the Guidelines on Good Clinical Practice for Trials on medicinal products in the European Community Directive 91/507/EEC and the Guidelines for Medical Experiments in non-patient human volunteers (ABPI 1988). All subjects gave informed written consent. An independent ethics committee had reviewed and approved the study protocol and all amendments.

### 2.2. Study design

The study was executed at a single centre (Cardiff Clinical Trials Ltd.) and consisted of two parts. The first part was a randomised, placebo-controlled, double-blind, crossover study to compare the cardiovascular effects of a single dose of tamsulosin MR capsule 0.4 mg in the fasted and the fed state. In the second part similar assessments were done in the fasted and fed state after multiple dosing of tamsulosin MR capsules 0.4 mg once daily (q.d.) or placebo for 14 days.

Each subject received one day of placebo run-in medication that was followed by randomisation to one of the single dose treatment groups (fasted or fed). After a wash-out of 7 days, the other treatment was administered. Following this second single-dosing day, the subjects continued the study medication for another 14 days at the end of which assessments in the fed and fasted state were repeated. A placebo control group was included throughout both parts of the study.

### 2.3. Study population (inclusion/exclusion criteria)

Male subjects aged 60 years and older with a systolic blood pressure (SBP) of 110 to (age + 100) mmHg, diastolic blood pressure (DBP) 70–95 mmHg) were eligible for recruitment. Subjects with medical conditions and/or chronic drug treatment not likely to interfere with the pharmacokinetics of tamsulosin could be included in the study. Subjects with heart disease, severe nervous system disease, renal or hepatic insufficiency, urological disease (except LUTS) and malignancies as well as subjects with a medical history of falling and with a positive symptomatic orthostatic test at screening were excluded form the study.

### 2.4. Treatments

Subjects were dosed in the morning 30 minutes after finishing a standard low-fat breakfast (cereals, 150 ml of milk, 2 rounds of toast, preserve spread and 150 ml of orange juice) for the fed group and in the same time frame for those subjects in the fasted group. Standard lunch and evening meals were provided to both groups 4 and 10 hours following dose administration respectively. Capsules of tamsulosin MR 0.4 mg or matching placebo capsules were given with 180 ml of water at room temperature.

### 2.5. Study procedure and criteria

Subjects remained in the clinical trial unit for the placebo run-in, baseline evaluation and first single dose assessment (Days 0–2), for the second single dose assessment (Days 7 and 8) and for the multiple dose assessments (Days 20 and 21). In the interim periods the subjects were at home. A post-study assessment visit was scheduled 1 to 2 weeks after the last visit.

### 2.6. Orthostatic stress tests and vital signs

Orthostatic stress tests were performed at screening, on Days 0, 1, 8, 20 and 21. On those days, the orthostatic stress test was performed at baseline and 4, 6 and 8 hours following drug administration, i.e. at times corresponding to trough and expected peak plasma concentrations of tamsulosin [20]. Blood pressure and pulse rate were measured after being supine for at least 5 minutes, subsequently after sitting for 2 minutes and finally after 3 minutes of relaxed standing (allowing the subject to walk if desired). The definition of a positive orthostatic stress test is described in Table 1. All additional vital signs measurements were done in the supine position. Arterial blood pressure was measured using a Hewlett Packard M1700A blood pressure/cardiac monitor device using the same arm throughout the study period. Vital signs were measured at the 0, 2, 4, 6, 8, 10, 12, 16 and 24-hour time points on the assessment days.

### 2.7. Assessments of safety/tolerability

Subjects were asked to report any symptoms experienced throughout the study. All AEs were subjected to a causality assessment and they were coded using the Coding System for a Thesaurus of Adverse Reaction Terms (COSTART) dictionary. Safety blood tests (biochemistry and haematology) were performed along with urinalysis during screening, on study days −1 and 22 and at the post-study visit.

### 2.8. Statistical methods

The change in vital functions in supine position during the study day was assessed by analysing the changes from baseline on a study day using a repeated measures analysis of variance at the 5%

**Table 1**
Definition of a positive orthostatic stress test

1. Symptoms such as light-headedness, dizziness, faintness, etc. upon standing, AND/OR
2. A decrease in SBP $\geq$20 mmHg between supine and standing posture, AND/OR
3. A decrease in DBP $\geq$10 mmHg between supine and standing and/or a standing DBP $<$60 mmHg, AND/OR
4. An increase in standing pulse rate $\geq$20 bpm between supine and standing and/or a standing pulse rate $\geq$100 bpm

**Table 2**
Mean demographic variables and vital signs by treatment group at study entry

| Variable | Tamsulosin MR 0.4 mg ($n = 24$) | Placebo ($n = 12$) |
|---|---|---|
| Age: years | 65.7 | 70.2 |
| Height: cm | 169.9 | 171.4 |
| Weight: kg | 77.7 | 82.5 |
| BMI: kg/m$^2$ | 26.9 | 28.2 |
| Supine SBP: mmHg | 142.8 | 139.5 |
| Supine DBP: mmHg | 83.5 | 75.1 |
| Supine pulse rate: bpm | 66.4 | 67.5 |
| Sitting SBP: mmHg | 146.1 | 137.8 |
| Sitting DBP: mmHg | 86.3 | 80.8 |
| Sitting pulse rate: bpm | 72.2 | 72.2 |
| Standing SBP: mmHg | 145.8 | 139.0 |
| Standing DBP: mmHg | 89.8 | 82.5 |
| Standing pulse rate: bpm | 74.0 | 75.0 |
| Respirations per minute | 16.2 | 15.8 |

significance level. The dependency of positive orthostatic stress tests on treatment and feeding state was investigated using a $\chi^2$-test. Logistic regression was used to look at both factors simultaneously.

## 3. Results

### 3.1. Demography and subject disposition

A total of 84 elderly male volunteers were screened of which 36 were enrolled in the study. All 36 subjects completed the study. The demographic data and the vital signs of the included subjects at study entry are presented in Table 2. Both the placebo group ($n = 12$) and the tamsulosin MR group ($n = 24$) were comparable with the exception of the DBP in supine and standing position.

### 3.2. Effects of tamsulosin MR 0.4 mg dosing on supine vital signs

The time courses of mean changes of SBP, DBP and pulse rate compared to baseline for all six treatments (placebo fasted and fed, tamsulosin MR single dose fasted and fed and tamsulosin MR multiple dose fasted and fed) are presented in Figs. 1–3. The changes in supine vital signs followed the expected diurnal pattern for all treatments with reductions in SBP and DBP and compensatory increases in pulse rate 2 h after lunch and dinner. Thus, SBP and DBP were smallest and pulse rate highest 6 and 12 h after dosing. Interestingly, the lunch and dinner-associated haemodynamic alterations tended to be larger in subjects which had taken their study medication in the fasted state, i.e. had not had breakfast. At most time points, SBP and DBP were slightly lower and pulse rate slightly higher in the tamsulosin MR than in the placebo group.

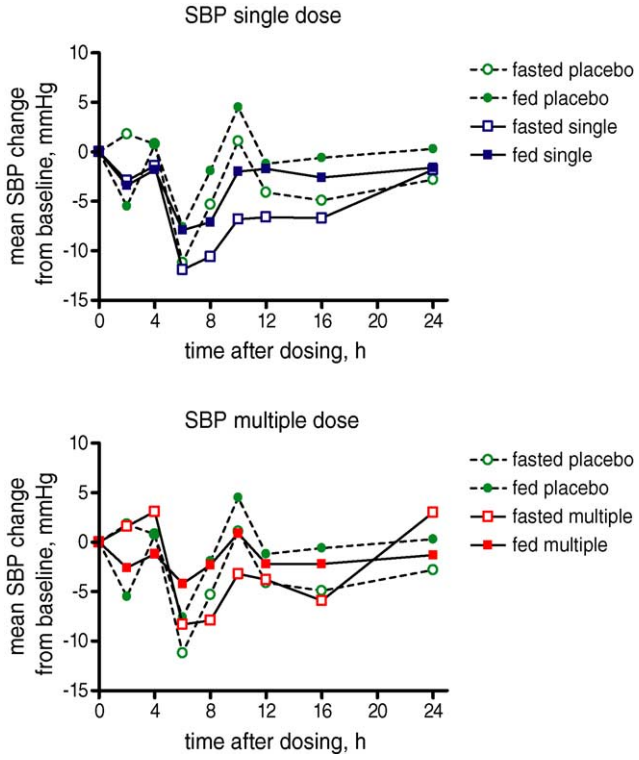


Fig. 1. Time course of mean changes from baseline in supine SBP in the fasted and fed states per treatment group. Single dose tamsulosin MR was assessed on Days 1 and 8, multiple dose was assessed on Days 20 and 21 and the placebo values were derived from a separate control group.

### 3.3. Effects on orthostatic blood pressure control

Orthostatic stress tests were executed on each assessment day (Days 1, 8, 20 and 21). Table 1 lists the criteria for judging an orthostatic stress test as being positive. A total of approximately 720 orthostatic tests were performed throughout the study (20 per subject). Table 3 presents the division of the 86 positive tests across the different groups. Of these 86 positive orthostatic tests only three were symptomatic: two after receiving the first dose of tamsulosin MR and one

**Table 3**
Number and percentage of subjects having at least one positive orthostatic test, by type of treatment and feeding state

| Treatment | Positive tests | Negative tests |
|---|---|---|
| Placebo, fasted | 10 (42%) | 14 (58%) |
| Placebo, fed | 17 (28%) | 43 (72%) |
| Tamsulosin single dose, fasted | 16 (67%) | 8 (33%) |
| Tamsulosin single dose, fed | 13 (54%) | 11 (46%) |
| Tamsulosin multiple dose, fasted | 18 (75%) | 6 (25%) |
| Tamsulosin multiple dose, fed | 12 (50%) | 12 (50%) |

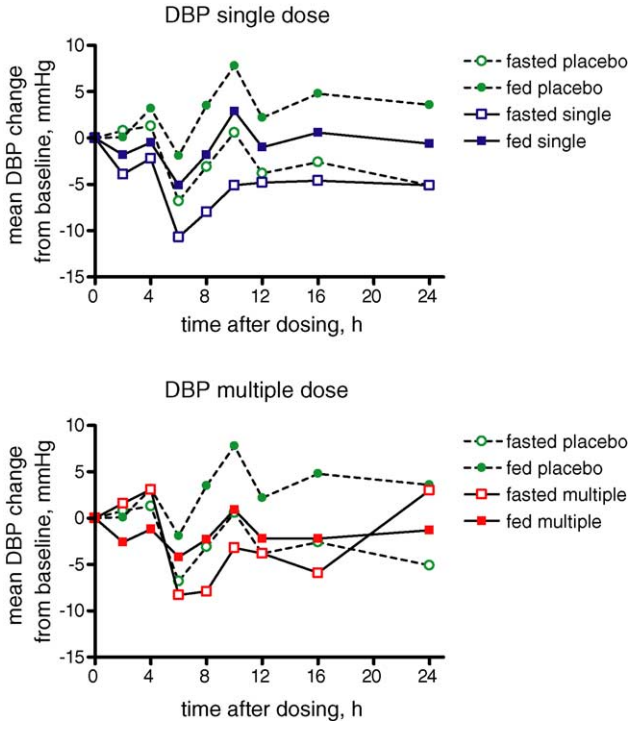


Fig. 2. Time course of mean changes from baseline in supine DBP in the fasted and fed states per treatment group. Single dose tamsulosin MR was assessed on Days 1 and 8, multiple dose was assessed on Days 20 and 21 and the placebo values were derived from a separate control group.

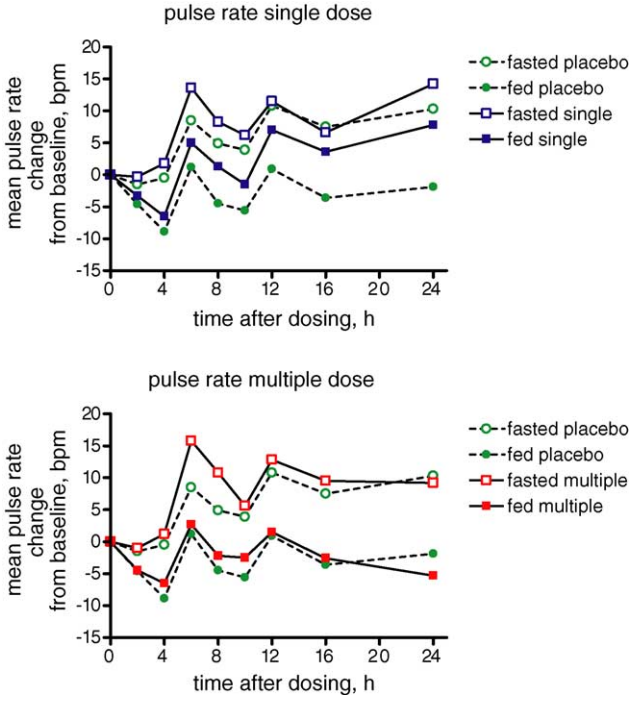


Fig. 3. Time course of mean changes from baseline in supine pulse rate in the fasted and fed states per treatment group. Single dose tamsulosin MR was assessed on Days 1 and 8, multiple dose was assessed on Days 20 and 21 and the placebo values were derived from a separate control group.

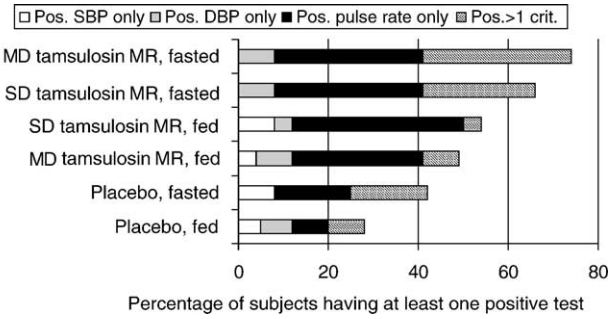


Fig. 4. Incidence and cause of positive orthostatic stress tests in the different treatment groups. Orthostatic stress tests were performed on the assessment days of the study (Days 1, 8, 20 and 21). The proportion of subjects having a positive test is indicated. SD: single dose; MD: multiple dose.

on Day 21 after receiving tamsulosin MR. One of the subjects with a first dose effect had moderately raised blood glucose before the study and the second had shown two asymptomatic positive orthostatic stress tests on the placebo run-in day.

The fasted state was associated with an increased incidence of positive orthostatic stress tests irrespective whether placebo or tamsulosin had been administered ($p = 0.028$, Fig. 4). Similarly, the administration of tamsulosin MR was also associated with an increased incidence of positive orthostatic stress tests; this was observed with both single and multiple dosing ($p = 0.0064$ and $p = 0.0032$ in the fasted and fed state, respectively, Fig. 4). Thus, subjects treated with tamsulosin MR in the fasted state had the greatest incidence of a positive orthostatic stress test (Fig. 4).

### 3.4. Safety/tolerability results

There were a total of 151 AEs reported by 33 subjects: 103 AEs in 21 (87.5%) subjects treated with tamsulosin MR and 48 AEs in 12 (100%) subjects treated with placebo. There were no serious AEs, and no subject withdrew from the study. 51 of the 103 AEs in the tamsulosin MR treated group and 18 of the 48 AEs in the placebo group were considered to be at least possibly related to treatment. Table 4 provides an overview of subjects with treatment emergent AEs, including AEs reported by the patient during the orthostatic stress testing. Headache was the most frequently reported AE by subjects both in the tamsulosin MR and placebo groups with a similar incidence. The AEs with the highest incidence on tamsulosin without a corresponding high incidence in the placebo group were abdominal pain, dizziness and dyspepsia. Only three subjects (all on tamsulosin MR) showed symptoms of orthostatic hypotension during the single dose ($n = 2$) or multiple dose ($n = 1$) phase of the study.

**Table 4**
Number of subjects with treatment emergent AEs by body system in the overall study, including those reported during the orthostatic stress tests

| AE: System organ class and COSTART preferred term | Tamsulosin ($n = 24$) | | Placebo ($n = 12$) | |
|---|---|---|---|---|
| | *n* | % | *n* | % |
| Body as a whole | | | | |
| Abdominal pain | 3 | 12.5 | | |
| Asthenia | 1 | 4.1 | | |
| Back pain | 1 | 4.1 | 3 | 12.5 |
| Chest pain | 1 | 4.1 | | |
| Flu syndrome | 1 | 4.1 | | |
| Headache | 15 | 62.5 | 8 | 66.6 |
| Hernia | | | 1 | 8.3 |
| Neck rigidity | 2 | 8.3 | 1 | 8.3 |
| Cardiovascular system | | | | |
| Migraine | 1 | 4.1 | | |
| Phlebitis | 1 | 4.1 | | |
| Nervous system | | | | |
| Dizziness | 5 | 20.8 | | |
| Hypertonia | 1 | 4.1 | | |
| Nervousness | 1 | 4.1 | | |
| Somnolence | 5 | 20.8 | 5 | 41.7 |
| Vertigo | 1 | 4.1 | 1 | 8.3 |
| Digestive system | | | | |
| Abnormal stools | | | 1 | 8.3 |
| Colitis | 1 | 4.1 | | |
| Constipation | 1 | 4.1 | | |
| Diarrhoea | | | 1 | 8.3 |
| Dyspepsia | 4 | 16.7 | 1 | 8.3 |
| Flatulence | 1 | 4.1 | 1 | 8.3 |
| Nausea | 5 | 20.8 | 5 | 41.7 |
| Tooth disorder | 1 | 4.1 | | |
| Vomiting | 2 | 8.3 | | |
| Respiratory system | | | | |
| Epistaxis | | | 1 | 8.3 |
| Rhinitis | | | 1 | 8.3 |
| Sputum increased | 1 | 4.1 | | |
| Metabolic/nutritional disorder | | | | |
| Hyperglycaemia | 1 | 4.1 | | |
| Musculoskeletal system | | | | |
| Arthralgia | 1 | 4.1 | 1 | 8.3 |
| Arthritis | 1 | 4.1 | 2 | 16.7 |
| Myalgia | 3 | 12.5 | 1 | 8.3 |
| Skin/appendages | | | | |
| Sweating | 2 | 8.3 | | |
| Urogenital system | | | | |
| Abnormal ejaculation | 1 | 4.1 | | |
| Incontinence | 1 | 4.1 | | |
| Urinary frequency | 3 | 12.5 | 1 | 8.3 |

## 4. Discussion

Over the last decade tamsulosin MR 0.4 mg has been established as a safe and efficacious treatment for LUTS/BPH. Direct and indirect comparisons with other $\alpha_1$-AR antagonists indicate a smaller incidence of cardiovascular side effects of tamsulosin, most importantly dizziness and symptomatic (orthostatic) hypotension. This superior tolerability profile is often ascribed to the relative selectivity for the $\alpha_{1A}$- and $\alpha_{1D}$-AR subtypes compared to the (vascular) $\alpha_{1B}$-AR subtype. In direct comparative studies of tamsulosin MR 0.4 mg q.d. using orthostatic stress testing it was demonstrated that tamsulosin MR (administered after breakfast) has a lower potential to induce symptomatic orthostatic hypotension than alfuzosin 5 mg twice daily and, even more so, than terazosin 1–5 mg q.d. [21,22].

The present study has been designed to see whether lack of compliance with the dosage instruction to take tamsulosin after breakfast or the first meal of the day could affect the cardiovascular safety.

Figs. 1–3 confirm the known physiological diurnal variation in blood pressure and pulse rate. They also show that SBP and DBP are lower and pulse rate is higher in subjects without breakfast. The haemodynamic effects of tamsulosin were small relative to the diurnal variation and the effects of breakfast, a finding which is not surprising considering the low sympathetic tone in the supine position. The lower blood pressure and higher pulse rate in subjects without breakfast should make them more vulnerable to orthostasis. Indeed we have observed a greater incidence of positive orthostatic tests in fasted subjects, and this was seen in the absence and presence of tamsulosin.

Catecholamine release and subsequent $\alpha_1$-AR stimulation are a key physiological mechanism to prevent orthostasis during postural changes. $\alpha_1$-AR antagonists counteract this physiological mechanism and hence can induce orthostasis. Accordingly, we have observed that tamsulosin MR 0.4 mg increased the number of positive orthostatic stress tests in both the fasted and fed state. This is a class effect of $\alpha_1$-AR antagonists and previous studies have shown it to be less pronounced with tamsulosin than with alfuzosin or terazosin [21,22].

The highest incidence of positive orthostatic stress tests was observed in subjects receiving tamsulosin MR 0.4 mg in the fasted state. The above physiological factors related to fasting and $\alpha_1$-AR antagonist use are likely to have contributed to that. Moreover, enhanced drug exposure due to increased bioavailability of tamsulosin upon administration in the fasted state appears to be another important contributor.

Taken together our data emphasize that the presently available MR formulation of tamsulosin must be taken after a meal in order to secure its well established

cardiovascular tolerability [13–20]. This appears most important in the elderly, since this population is particularly vulnerable to orthostasis [23].

## 5. Conclusions

The administration of tamsulosin MR capsules 0.4 mg in the fasted state is associated with a higher incidence of positive orthostatic stress tests. Therefore, the good tolerability of the presently available tamsulosin formulation depends at least partly on compliance with the recommended dosing after the first meal of the day.

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