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The Improved Cardiovascular Safety of Omnic (Tamsulosin) Oral Controlled Absorption System (OCAS®)

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1. Introduction

The oral controlled absorption system (OCAS®) is a new improved formulation/delivery system of tamsulosin, called Omnic OCAS. Omnic OCAS gels rapidly and hydrates completely in the upper gastro-intestinal (GI) tract which ensures continuous and consistent drug release throughout the entire length of the GI tract, also in the colon where water is poorly available [1,2]. This leads to improved pharmacokinetics (PK) of Omnic OCAS compared to the existing conventional tamsulosin formulation: (1) lower maximum plasma concentration (C_{max}), (2) more consistent 24-hour plasma concentration or improved C_{max}/C_{24h} ratio and (3) independence of PK of food intake [1,2]. Double-blind, randomised, placebo and active comparator controlled phase 2b-3a clinical registration studies have shown that Omnic OCAS 0.4 mg once daily (q.d.) is the recommended dose [3–5]. In clinical studies, the incidence of adverse events (AEs), in particular those commonly associated with α_1-adrenoceptor (AR) antagonists, is slightly lower with Omnic OCAS 0.4 mg than with the conventional tamsulosin 0.4 mg q.d. formulation [4–5]. Therefore, these data from registration studies point at a more favourable efficacy/tolerability profile for Omnic OCAS 0.4 mg q.d. compared to conventional tamsulosin 0.4 mg q.d.

2. Optimal measurement of cardiovascular safety of α_1-adrenoceptor antagonists

Standard randomised controlled clinical studies are likely to underestimate the occurrence of AEs commonly associated with α_1-AR antagonists, in particular those related to the cardiovascular system, and therefore the real difference in cardiovascular safety between α_1-AR antagonists in daily life. This is amongst others due to the facts that the very elderly and patients with cardiovascular co-morbidity and/or taking vasodilatatory co-medication who are in particular prone to interference with blood pressure control by α_1-AR antagonists are largely excluded from these

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trials. Furthermore, situations such as standing up, exercising, a heavy meal, heat stress (taking a hot bath or hot climates) and dehydration (e.g. following diarrhoea), which further challenge or stress the cardiovascular system, occur in daily life, but are not frequently observed during routine office visits unless specific provocation tests are done. Dizziness and orthostatic hypotension are not only unpleasant for the patient, but they can also be dangerous as they can lead to serious morbidity such as falls and fractures potentially resulting in hospitalisation, nursing home placement and/or death [6,7]. Therefore, the potential risk of orthostatic hypotension when taking an α_1-AR antagonist in daily life should be optimally assessed and minimised as far as possible.

Cardiovascular effects of α_1-AR antagonists are detected most sensitively during dedicated studies with provocation tests that challenge or stress the cardiovascular system. Therefore, such tests are used as models for predicting the risk of orthostatic hypotension in daily life in the mentioned higher risk patient groups [8].

3. Cardiovascular safety of Omnic OCAS

Two specific phase 3b studies were designed to evaluate the difference in cardiovascular safety between Omnic OCAS 0.4 mg and conventional tamsulosin 0.4 mg under fasted conditions which might be relevant in daily life.

The first study was a randomised, double-blind, cross-over study in 18 young, healthy volunteers in which the effects of endogenous α_1-AR stimulation by noradrenaline and adrenaline (the two endogenous sympathetic agonists that are released during e.g. exercising or posture change) were mimicked by infusing the synthetic α_1-AR agonist phenylephrine (PE) [9]. This increases diastolic blood pressure (DBP) and total peripheral resistance (TPR). By gradually increasing infusion speed, or dose given in a time interval, a dose-dependent increase in DBP and TPR results and a dose-response curve can be drawn for each subject. The degree of inhibition of the PE-induced increase in DBP and TPR (right shift of the dose-response curve) is a measure of the cardiovascular α_1-AR antagonism of a drug: the larger the inhibition of the PE-induced increase in DBP and TPR, i.e. the higher the dose of PE required to increase the DBP or TPR to a certain extent, the more the α_1-AR antagonist blocks α_1-ARs in the vascular system [10]. PE infusions were made 2 hours before and 2, 4, 6, 8 and 10 hours after dosing. It appeared that at all post-dose time points under fasting conditions a single dose of Omnic OCAS 0.4 mg induced less inhibition of PE-induced increases in DBP (Fig. 1) and TPR than a single dose of conventional tamsulosin 0.4 mg. Omnic OCAS 0.4 mg thus exhibited less vascular α_1-AR antagonism than conventional tamsulosin 0.4 mg.

The second study was a randomised, double-blind, cross-over study in 40 healthy, elderly subjects in which the cardiovascular system was challenged by orthostatic stress tests by provoked posture changes at regular time points [11]. A higher incidence of positive orthostatic stress tests represents a larger cardiovascular α_1-AR antagonism of a drug. Orthostatic stress tests were done at 30 minutes before dosing and at 4, 6 and 8 hours after dosing. The definition of a positive orthostatic stress test is given in Table 1. At all time points under fasting conditions, the incidence of a positive orthostatic stress test outcome following a single dose of Omnic OCAS 0.4 mg was numerically lower than

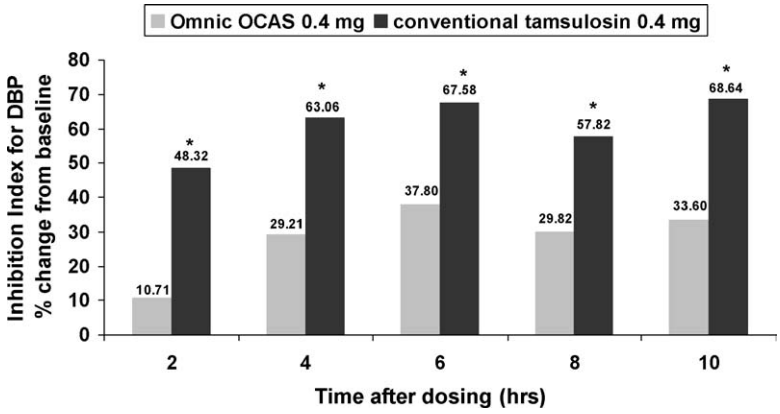

Fig. 1. Omnic OCAS 0.4 mg induces less inhibition of PE-induced increases in DBP than conventional tamsulosin 0.4 mg.
* $P < 0.05$ for conventional tamsulosin 0.4 mg vs. Omnic OCAS 0.4 mg. Reprinted from European Urology Supplements, 4(2), Michel MC, Korstanje C, Krauwinkel W, Shear M, Davies J, Quartel A, Comparison of vascular α_1-adrenoceptor antagonism of tamsulosin in oral controlled absorption system (OCAS) and modified release formulations, pp 45–52, 2005, with permission from European Association of Urology [9].