

## Tamsulosin and urinary incontinence

### Introduction

Tamsulosin hydrochloride (Omnice<sup>®</sup>) is an antagonist of  $\alpha_1$ -adrenoceptors in the prostate. Tamsulosin is indicated for *the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)*. It is also used off-label for the treatment of nephrolithiasis in women [1]. Tamsulosin has been approved for the Dutch market since April 1995 [2].

The symptoms associated with benign prostatic hyperplasia (BPH) are related to bladder outlet obstruction, which is comprised of two underlying components: static and dynamic. The static component is related to an increase in prostate size caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. The dynamic component is a function of an increase in smooth muscle tone in the prostate and bladder neck leading to constriction of the bladder outlet. Smooth muscle tone is mediated by the sympathetic nervous stimulation of  $\alpha_1$  adrenoceptors, which are abundant in the prostate, prostatic capsule, prostatic urethra, and bladder neck. Blockade of these adrenoceptors can cause smooth muscles in the bladder neck and prostate to relax, resulting in an improvement in urine flow rate and a reduction in symptoms of BPH. In clinical practice tamsulosin is also used off-label for the treatment of nephrolithiasis.

Tamsulosin exhibits selectivity for  $\alpha_1$ -receptors in the human prostate. At least three discrete  $\alpha_1$ -adrenoceptor subtypes have been identified:  $\alpha_{1A}$ ,  $\alpha_{1B}$ , and  $\alpha_{1D}$ ; their distribution differs between human organs and tissue. Approximately 70% of the  $\alpha_1$ -adrenoreceptors in the human prostate are of the  $\alpha_{1A}$  subtype [3]. Other selective  $\alpha_1$ -antagonists for the treatment of BPH on the Dutch market are alfuzosin (Xatral<sup>®</sup>), doxazosin (Cardura<sup>®</sup>), silodosin (Silodyx<sup>®</sup>) and terazosin (Hytrin<sup>®</sup>).

Urinary incontinence often has an identifiable cause in younger persons. In older persons a multifactorial syndrome is more likely. Neuro-urinary pathology, age-related factors, comorbid conditions, medications, and functional and cognitive impairments may play a role in the older population [4].

The current observation describes the association between tamsulosin and urinary incontinence. No reports for incontinence associated with other  $\alpha_1$ -adrenoceptor antagonists were received by Lareb. Therefore, a possible class effect was not investigated.

### Reports

On April 11<sup>th</sup> 2014, the database of the Netherlands Pharmacovigilance Centre Lareb contained eleven reports of incontinence associated with the use of tamsulosin. The reports are listed in table 1.

Table 1. Reports of urinary incontinence associated with the use of tamsulosin

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 24881 M, 61-70 years	tamsulosin 0.4mg 1dd hyperplasia of prostate		urinary incontinence, rash	not reported unknown not reported

Pharmacist				
B 41722 M, 61-70 years General Practitioner	tamsulosin 0.4mg 1dd not reported		urinary incontinence	3 days discontinued recovered positive rechallenge
C 44261 M, 61-70 years Consumer	tamsulosin 0.4mg 1dd hyperplasia of prostate	allopurinol	urinary incontinence	not reported unknown not recovered
D 52650 M, 71 years and older Pharmacist	tamsulosin 0.4mg 1dd	hydrochlorothiazide with quinapril pyridoxine calcium levothyroxine carbasalate calcium folic acid dihydrotachysterol	urinary incontinence, therapeutic response unexpected with drug substitution	not reported no change unknown
E 72129 F, 51-60 years Pharmacist	tamsulosin 0.4mg 1dd kidney stone	diclofenac allopurinol zopiclone	incontinence	3 days no change recovered positive rechallenge
F 107476 M, 51-60 years Pharmacist	tamsulosin 0.4mg 1dd benign prostatic hyperplasia		incontinence of urine	2 months discontinued not recovered
G 129137 M, 51-60 years Consumer	dutasteride/tamsulosin 0,5/0,4mg 1dd benign prostatic hyperplasia		Incontinence, ejaculation failure	2 months no change not recovered
H 145200 F, 51-60 years Specialist doctor	tamsulosin 0.4mg 1dd stone urinary bladder	hydrochlorothiazide	incontinence of urine	several days discontinued recovered
I 147585 M, 61-70 years Pharmacist	tamsulosin 0.4mg 1dd benign neoplasm of prostate	losartan	incontinence, headache, tremor, urticaria, hot flush, palpitations, rhinorrhea	1 day discontinued recovered
J 160773 M, 61-70 years Pharmacist	tamsulosin 0.4mg 1dd lower abdominal pain	leuprorelin	urinary incontinence	5 days discontinued recovered
K 168760 M, 71 years and older Pharmacist	tamsulosin 0.4mg 1dd benign prostatic hyperplasia	colecalfiferol urea mometasone	urinary incontinence, fecal incontinence, therapeutic response unexpected with drug substitution	4.5 years discontinued recovered

Additional information about the cases is described below:  
In case A, the complaints were reported as urge incontinence.

In case B, both a positive de- and rechallenge were reported. Additionally, the patient ceased his excessive consumption of alcohol (gamma-GT value of 280 U/l) after starting tamsulosin.

In case C, the patient experienced the complaints related to stress incontinence (blowing his nose).

In case D, the complaints arose when the patient was switched from capsules to tablets.

In case E, the patient experienced similar problems in the past.

In case F, the patient had not recovered at the time of reporting, which was 6 days after withdrawal of tamsulosin.

In case G, the patient switched to separate preparations of dutasteride and alfuzosin and experienced the same complaints. The patient previously used tamsulosin without dutasteride and experienced the ejaculation disorder.

Incontinence was not reported for this episode of tamsulosin use.

In case I, the patient was treated with cetirizine for his urticaria, and recovered from all complaints two days after withdrawal of tamsulosin.

In case J, the patient had a history of prostate cancer for which he underwent surgery. He previously used tamsulosin without experiencing any complaints.

In case K, the patients switched from the Ranbaxy brand (which he had been using for approximately 2 years) to the Mylan brand and his complaints disappeared quickly.

## Other sources of information

### SmPC

Urinary incontinence is not mentioned in the SmPC of tamsulosin [2].

### Literature

Urinary incontinence has been described as an adverse effect in women using tamsulosin. In a prospective study with 106 patients with voiding dysfunction, three patients developed de novo stress incontinence and one patient experienced an aggravation of an existing stress incontinence [5]. Furthermore, a study with  $\alpha_1$ -adrenoceptors other than tamsulosin (prazosin, terazosin and doxazosin) showed a statistically significant higher percentage of urinary incontinence in patients using  $\alpha_1$ -adrenoceptors compared to matched controls [6]. Studies investigating this association in male patients could not be found.

### Databases

Table 2. Reports of (urinary) incontinence with tamsulosin (with or without dutasteride) in the databases of the Netherlands Pharmacovigilance Centre Lareb and the WHO [7] and Eudravigilance (EMA) database [8].

Database	Preferred Terms	Number of reports	ROR (95% CI)
Lareb	Urinary incontinence	8	7.2 (3.5 – 14.6)
	Incontinence	3	18.3 (5.6 – 59.3)
	Total	11	8.7 (4.7 – 15.9)
WHO	Urinary incontinence	103	5.1 (4.2 – 6.1)
	Incontinence	30	9.3 (6.5 – 13.3)
	Total	133	5.7 (4.8 – 6.7)
Eudravigilance	Urinary incontinence	31	3.5 (2.5 – 5.0)

Database	Preferred Terms	Number of reports	ROR (95% CI)
	Incontinence	12	4.5 (2.6 – 8.0)
	Total	43	3.8 (2.8 – 5.1)

### Prescription data

Table 3. Number of patients using tamsulosin in the Netherlands between 2009 and 2013 [9].

Drug	2009	2010	2011	2012	2013
Tamsulosin	172,950	186,450	194,660	199,250	205,890
Tamsulosine / dutasteride	-	5,723	19,438	28,787	34,019

### Mechanism

Tamsulosin binds selectively and competitively to the postsynaptic  $\alpha_1$ -adrenoreceptors, in particular to the subtype  $\alpha_{1A}$  and  $\alpha_{1D}$  [2]. It is known that  $\alpha_1$ -adrenergic receptors are present in both the detrusor muscle [10] and the bladder sphincter [11]. The antagonistic effect of tamsulosin on the  $\alpha_1$ -adrenergic receptors of the bladder could therefore theoretically result in both urinary retention and incontinence, depending on the exact affinity of the drug for each receptor subtype and their ratios in sphincter and detrusor. A functional urodynamic study however, showed that tamsulosin had a significant relaxing effect on the resting urethral tone, suggesting a pharmacological treatment for urinary retention [12]. Urinary incontinence could therefore be seen as a possible detrimental effect of this pharmacological mechanism.

### Discussion and conclusion

Lareb received eleven cases of urinary incontinence associated with the use of tamsulosin. The reports concern nine males and two females. In five cases a positive dechallenge was reported and in two cases a positive rechallenge, which support the causality of this association. However, there was also one negative dechallenge. In one case the complaints arose after switching to another brand and in one case after switching to another formulation (tablets to capsules of the same brand). This association was disproportionality present in the Lareb, WHO and Eudravigilance databases, has been described in literature and seems pharmacologically plausible. In addition to the previously described literature, a case report of a woman experiencing stress urinary incontinence after starting doxazosin was found [13]. This case shows similarities with our case C who also experienced stress incontinence, indicating that the complaints are possibly not due to confounding by indication (BPH). Although the articles found in the literature are limited to studies in female patients, our data suggest that male patients could also experience these symptoms.

Although BPH could be considered as a possible confounder, these patients often experience overflow incontinence. This is however not mentioned in any of the described cases. Moreover, in two cases (E,H) this can be ruled out since the patients are female, whereas two other cases (A,C) specifically mention urge and stress incontinence respectively. Age however, could be a possible confounding factor in this association.

- Urinary incontinence should be mentioned in the SmPC of tamsulosin

## References

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*This signal has been raised on October 2014. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB [www.cbqmeb.nl/cbq/en/default.htm](http://www.cbqmeb.nl/cbq/en/default.htm)*

*The Marketing Authorization Holder of tamsulosin (Astellas) has informed Lareb on 07-10-2014 of the following: After careful evaluation of the signal report tamsulosin and urinary incontinence, the Marketing Authorization Holder, is of the opinion that there is no sufficient evidence to support a causal relationship between tamsulosin and urinary incontinence. An addition of a warning for urinary incontinence to the SmPC is therefore not warranted, according to Astellas.*