

## Tamsulosin and erectile dysfunction

### Introduction

Tamsulosin hydrochloride (Omnice<sup>®</sup>) is an antagonist of alpha1A adrenoceptors in the prostate. Tamsulosin is indicated for *the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)*. It has been approved for the Dutch market since April 1995 [1].

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 alpha1 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.

Tamsulosin exhibits selectivity for alpha1 receptors in the human prostate. At least three discrete alpha1 adrenoceptor subtypes have been identified: alpha1A, alpha1B, and alpha1D; their distribution differs between human organs and tissue. Approximately 70% of the alpha1 receptors in the human prostate are of the alpha1A subtype [2].

Other selective alpha1-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>).

Erectile dysfunction has been defined as the persistent inability to reach or maintain penile rigidity enough for sexual satisfaction. Erectile dysfunction has a high prevalence and a huge impact on quality of life of men and their partners. Common risk factors associated with sexual dysfunction include individual general health status, diabetes mellitus, cardiovascular disease, other genitourinary disease, psychiatric/psychological disorders, other chronic disease, socio-demographic conditions and the use of certain drugs [3].

The current observation describes the association between tamsulosin and erectile dysfunction.

### Reports

On August 2<sup>nd</sup> 2013, the database of the Netherlands Pharmacovigilance Centre Lareb contained fourteen reports of erectile dysfunction associated with the use of tamsulosin. Ten patients reported impotence and four patients reported a decreased erection. All patients used tamsulosin 0,4 mg once daily for the treatment of BPH. The median age was 66 years and ranged from 51 to 74 years. Time to onset varied from 1 day to several weeks, but the erectile dysfunction was mostly present after one to three days use of tamsulosin. Eight patients recovered after stopping treatment with tamsulosin. One patient reported the same problems after restart of tamsulosin weeks later. Three patients continued the use of tamsulosin and did not recover and the other three patients did not report the

outcome. Six patients reported co-medication known to cause erectile dysfunction such as simvastatin, irbesartan/hydrochlorothiazide, dutasteride, perindopril and allopurinol. However, these drugs had been used for years before start of tamsulosin and four patients recovered after stopping treatment with tamsulosin and were still using these other drugs.

## Other sources of information

### SmPC

The SmPC of tamsulosin does not mention erectile dysfunction. Only priapism and ejaculation disorders are mentioned [1]. The SmPCs of doxazosin and terazosin mention impotence and the SmPC of silodosin mentions erectile dysfunction.

### Literature

Decreases in erectile function have been described as adverse events in studies assessing the efficacy and tolerability of alpha-blockers.

In a randomized controlled trial 131 patients received 0.4 mg tamsulosin once daily and 124 patients received 2.5 mg alfuzosin three times daily during 12 weeks. Of the patients using tamsulosin 3.1% reported impotence compared to 2.4% of the patients using alfuzosin [4].

In a randomized placebo controlled trial the incidence of impotence was 4.4% in the tamsulosin group (158 patients, 0.4 mg tamsulosin once daily for 12 weeks) and 0% in the placebo group (153 patients) ( $P < 0.001$ ) in men with benign prostatic hyperplasia [5].

In a study in which the long-term efficacy and safety of 0.4mg tamsulosin once daily were assessed in 516 patients for up to four years, impotence was reported in 5.4% of the patients [6].

In a long-term open-label phase III multicenter study of tamsulosin 949 patients received 0.4 mg tamsulosin once daily. Impotence was reported in 6.3% of the patients [7].

In contrast to our current finding, other studies report a beneficial effect of tamsulosin on sexual function. These studies suggest that tamsulosin may contribute to an improvement in erectile function [8,9].

### Databases

On August 7<sup>th</sup> 2013, the database of the Netherlands Pharmacovigilance Centre Lareb contained fourteen reports of erectile dysfunction associated with the use of tamsulosin which was reported disproportionately. Furthermore, the Lareb database contained five reports of erectile dysfunction for alfuzosin and three reports for doxazosin. The reporting odds ratios are shown in table 1.

Table 1. Reports of erectile dysfunction for the selective alpha1-antagonists in the Lareb database.

Drug	Number of reports	ROR (95% CI)
tamsulosin	14	5.7 (3.4-9.6)
alfuzosin	5	4.2 (1.7-10.2)
doxazosin	3	3.9 (1.2-12.1)
selective alpha1-antagonists total	22	5.1 (3.3-7.7)

The WHO database of the Uppsala Monitoring Centre contained 169 reports of erectile dysfunction associated with the use of tamsulosin. This association is disproportional.

Table 2 shows the number of reports of erectile dysfunction associated with the use of tamsulosin and other selective alpha1-antagonists in the WHO database.

Table 2. Reports of erectile dysfunction for the selective alpha1-antagonists in the WHO database.

Drug	Number of reports	ROR (95% CI)
tamsulosin	169	6.5 (5.6-7.6)
alfuzosin	49	6.0 (4.5-7.9)
doxazosin	154	7.1 (6.1-8.4)
terazosin	102	6.3 (5.2-7.6)
silodosin	18	11.9 (7.5-19.1)
selective alpha1-antagonists total	492	6.8 (6.2-7.4)

On August 13<sup>th</sup> 2013, the Eudravigilance database contained 51 reports of erectile dysfunction in association with tamsulosin, which was reported disproportionately (ROR=9.7, 95% CI: 7.3-12.8). The number of reports of erectile dysfunction for all selective alpha1-antagonists is given in Table 3.

Table 3. Reports of erectile dysfunction for the selective alpha1-antagonists in the Eudravigilance database.

Drug	Number of reports	ROR (95% CI)
tamsulosin	51	9.7 (7.3-12.8)
alfuzosin	10	6.8 (3.7-12.7)
doxazosin	9	3.8 (2.0-7.4)
terazosin	6	9.7 (4.3-21.7)
silodosin	5	10.7 (4.4-26.0)
selective alpha1-antagonists total	81	8.1 (6.5-10.1)

## Prescription data

The number of patients using selective alpha1-antagonists in the Netherlands is shown in Table 4.

Table 4. Number of patients using selective alpha1-antagonists in the Netherlands between 2008 and 2012 [10].

Drug	2008	2009	2010	2011	2012
tamsulosin	162,100	172,950	186,450	194,700	198,500
doxazosin	40,016	39,767	40,922	41,650	42,859
terazosin	2,172	1,951	1,731	1,587	1,419
alfuzosin	62,833	60,572	59,916	57,194	53,733
silodosin	-	-	-	1,292	4,178

## Mechanism

Tamsulosin binds selectively and competitively to postsynaptic alpha1-adrenoceptors, mostly subtype alpha1A. This causes relaxation of the smooth muscle in the prostate and urethra. Postsynaptic alpha1A-adrenoceptors are also present in arterioles and veins. Blockade of alpha1-adrenoceptors in the arterioles and veins causes dilatation [11]. To obtain an erection blood-supply to the penis must be adequate and blood-outflow must be delayed. Probably the dilatation of the veins results in blood-outflow from the penis and therefore in an inability to obtain/maintain an erection [12].

### *Class effect*

The Lareb database contains five reports of erectile dysfunction for alfuzosin and three reports for doxazosin. The WHO and the Eudravigilance database contain numerous reports of erectile dysfunction associated with the use of selective alpha1-antagonists. All associations are reported disproportionally (Table 1, 2 and 3). Since all the selective alpha1-antagonists have the same mechanism of action it would seem plausible that erectile dysfunction is a class effect. Furthermore, erectile dysfunction is already mentioned in the SmPC of doxazosin, terazosin and silodosin.

## Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received fourteen reports of erectile dysfunction associated with the use of tamsulosin. Erectile dysfunction was mostly present after several days of tamsulosin use.

Erectile dysfunction is highly prevalent in men with lower urinary tract symptoms and is strongly related to increasing age [13]. Prevalence of erectile dysfunction increases from 14% in 41-50 year old men to 42% in 71-80 year old men [14]. All patients reported to Lareb were being treated for benign prostatic hyperplasia and were 51 to 74 years old. However, there were eight patients who reported recovery after stopping tamsulosin treatment.

The association of tamsulosin with erectile dysfunction is supported by a statistically significant disproportionality in the databases of Lareb, the WHO and Eudravigilance. This is also the case for the other selective alpha1-antagonists. Although studies reported in the literature of alpha1-antagonists on erectile function are inconsistent, with both adverse and beneficial effects being reported, impotence can occur in some patients. Probably the blood pressure lowering effect of alpha-blockers can be associated with adverse effects on erectile function.

- Erectile dysfunction should be mentioned in the SmPC of tamsulosin

## References

1. Dutch SmPC Omnic<sup>®</sup>. (version date: 6-2-2012, access date: 19-10-2012) <http://db.cbg-meb.nl/IB-teksten/h17931.pdf>.
2. US SmPC Flomax<sup>®</sup>. (version date: 25-7-2011, access date: 31-10-2012) [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2011/020579s027lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020579s027lbl.pdf).
3. Javaroni V, Neves MF. Erectile dysfunction and hypertension: impact on cardiovascular risk and treatment. *Int.J.Hypertens.* 2012;2012:627278
4. Buzelin JM, Fonteyne E, Kontturi M, Witjes WP, Khan A. Comparison of tamsulosin with alfuzosin in the treatment of patients with lower urinary tract symptoms suggestive of bladder outlet obstruction (symptomatic benign prostatic hyperplasia). The European Tamsulosin Study Group. *Br.J.Urol.* 1997;80(4):597-605.
5. 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(7):1006-12.
6. Schulman CC, Lock TM, Buzelin JM, Boeminghaus F, Stephenson TP, Talja M. Long-term use of tamsulosin to treat lower urinary tract symptoms/benign prostatic hyperplasia. *J.Urol.* 2001;166(4):1358-63.
7. Narayan P, Lepor H. Long-term, open-label, phase III multicenter study of tamsulosin in benign prostatic hyperplasia. *Urology* 2001;57(3):466-70.
8. Jo HW, Yoo DS, Ju HT, Whang HW, Park J, Kim ET, Kim DK, Woo SH. Effect of patient-optimized doses of tamsulosin on erectile function in men with erectile dysfunction and lower urinary tract symptoms. *Korean J.Urol.* 2013;54(2):100-5.
9. Shelbaia A, Elsaied WM, Elghamrawy H, Abdullah A, Salaheldin M. Effect of Selective Alpha-blocker Tamsulosin on Erectile Function in Patients With Lower Urinary Tract Symptoms due to Benign Prostatic Hyperplasia. *Urology* 2013;82(1):130-5.
10. GIPdatabase - Drug Information System of the Dutch Health Care Insurance Board. (version date: 15-5-2012, access date: 19-10-2012) <http://www.gipdatabank.nl>.
11. KNMP/Winap. Informatarium Medicamentorum. (version date: 1-10-2012, access date: 22-10-2012) <http://kennisbank.knmp.nl/index.asp#IMG657>.
12. Erectiele disfunctie. (version date: 2003, access date: <http://www.merckmanual.nl/mmhnl/sec21/ch240/ch240b.html>).
13. Vallancien G, Emberton M, Harving N, van Moorselaar RJ. Sexual dysfunction in 1,274 European men suffering from lower urinary tract symptoms. *J.Urol.* 2003;169(6):2257-61.
14. NHG-Standaard Erectiele disfunctie. (version date: 2008, access date: [https://www.nhg.org/sites/default/files/content/nhg\\_org/uploads/standaard/download/m87.pdf](https://www.nhg.org/sites/default/files/content/nhg_org/uploads/standaard/download/m87.pdf)).

After evaluating this signal, the marketing authorization holder of tamsulosin, Astellas Pharma, has informed the Netherlands Pharmacovigilance Centre Lareb on 05-02-2014 that a causal association between tamsulosin and erectile dysfunction cannot be established based on the available information.

*This signal has been raised on 31 October 2013. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB [www.cbgmeb.nl/cbg/en/default.htm](http://www.cbgmeb.nl/cbg/en/default.htm) or the responsible marketing authorization holder(s).*