

Lower urinary tract symptoms secondary to benign prostatic hyperplasia: tadalafil

Evidence summary

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Overview

The content of this evidence summary was up-to-date in May 2013. See [summaries of product characteristics](#) (SPCs), [British national formulary](#) (BNF) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Key points from the evidence

Tadalafil is a reversible phosphodiesterase type 5 inhibitor available as an oral tablet in various strengths. In October 2012, the 5 mg tadalafil tablet (taken once daily) was granted marketing authorisation to treat signs and symptoms of benign prostatic hyperplasia in adult men. Other strength tablets (2.5 mg, 5 mg, 10 mg and 20 mg) already have marketing authorisation to treat erectile dysfunction in adult men.

The main drug treatments currently recommended in the NICE pathway on [lower urinary tract symptoms in men](#) are alpha blockers and 5-alpha reductase inhibitors. Tadalafil (5 mg only) represents an additional treatment option and is the only drug in its class licensed for treating signs and symptoms of benign prostatic hyperplasia. Assessing tadalafil's likely place in therapy in relation to current drug treatment is difficult because there are few published randomised trials of its use in first-line, second-line or combination treatment compared with current best practice.

This evidence summary is based on 2 studies of tadalafil that have been published in full. The first ([Roehrborn et al. 2008](#)) was a large (1058 men), double-blind, placebo-controlled, dose-finding

randomised controlled trial (RCT) comparing various strengths of tadalafil monotherapy once daily with placebo for 12 weeks (212 men were assigned the tadalafil 5 mg dose). After the 12-week study ended, 427 men elected to take part in a second, 1-year, open-label extension study ([Donatucci et al. 2011](#)) that used tadalafil 5 mg daily monotherapy. This 5 mg dose was used regardless of initial treatment in the 12-week study.

Tadalafil 5 mg daily improved lower urinary tract symptoms compared with placebo after 12 weeks of treatment (an average [mean] 2.6 point additional improvement in overall International Prostate Symptoms Score [I-PSS]) compared with placebo. While this difference was statistically significant, a clinically meaningful improvement in score is defined in the study as a 3-point improvement in I-PSS from baseline. Other statistically significant improvements over placebo were seen for I-PSS obstructive subscore, I-PSS irritative subscore and I-PSS quality of life. Most of the primary benefits associated with tadalafil occurred within the first 12 weeks of treatment and were maintained or improved to a much smaller degree for up to 1 year.

During the 1-year [open-label extension study](#), 4.7% of men receiving tadalafil 5 mg daily reported severe adverse events, 5.2% reported adverse events leading to discontinuation, and 57.6% reported 1 or more treatment-emergent adverse events of any severity.

A 28-tablet pack of tadalafil 5 mg costs £54.99; this represents the approximate monthly cost of the drug treatment.

When making decisions about the use of tadalafil, localities will need to take this evidence of marginal clinical effectiveness into account alongside the one year data on tolerability. The acquisition cost of tadalafil is also higher than other treatment options. The prescribing of tadalafil for erectile dysfunction in England is subject to statutory prescribing restrictions through Schedule 2 of the NHS (general medical services contracts) (prescription of drugs etc.) regulations 2004 and the NHS (Pharmaceutical and Local Pharmaceutical Services) Regulations 2013. These prescribing restrictions do not apply to tadalafil when it is prescribed in primary care on the NHS for benign prostatic hyperplasia (Department of Health: personal communication October 2013).

Key evidence

Roehrborn CG, McVary KT, Elion-Mboussa A et al. (2008) [Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a dose finding study](#).

The Journal of Urology 180: 1228–34

Donatucci CF, Brock GB, Goldfischer ER et al. (2011) [Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a 1-year, open-label extension study](#). British Journal of Urology International 107: 1110–6

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

Relevance to NICE guidance programmes

[Tadalafil for the treatment of symptoms associated with benign prostatic hyperplasia \(terminated appraisal\) \(NICE technology appraisal 273\)](#) was referred to NICE for a technology appraisal in July 2012. However, NICE terminated the appraisal in January 2013 and was unable to recommend the use of tadalafil in the NHS for treating symptoms associated with benign prostatic hyperplasia because no evidence submission was received from the manufacturer of the technology.

In May 2010, NICE issued a clinical guideline on [the management of lower urinary tract symptoms in men](#) (NICE clinical guideline 97), which has also been incorporated into a NICE pathway on [lower urinary tract symptoms in men](#).

Introduction

The NICE clinical guideline on [lower urinary tract symptoms in men](#) (LUTS) states that LUTS comprise storage, voiding and post-micturition (after urination) symptoms affecting the lower urinary tract. There are many possible causes of LUTS, such as abnormalities or abnormal function of the prostate, urethra, bladder or urinary sphincters. In men, one of the most common causes is benign prostate enlargement, which obstructs the bladder outlet. Benign prostate enlargement occurs when the number of cells in the prostate increases: a condition called benign prostatic hyperplasia.

The NICE pathway on [LUTS in men](#) advises conservative management after initial assessment of LUTS. If overactive bladder is suspected, supervised bladder training, advice on fluid intake, lifestyle advice and containment products are recommended.

The [full guideline for LUTS](#) defines bothersome symptoms as symptoms that are worrying, troublesome or have an impact on quality of life from the patient's perspective. For men with bothersome symptoms and when conservative management options have been unsuccessful or are not appropriate, the NICE pathway on [LUTS in men](#) advises offering drug treatments, but did not make any recommendations around the use of phosphodiesterase type 5 inhibitors such as tadalafil. The recommended drug treatment options vary depending on the specific symptoms and their severity and include:

- An alpha blocker (alfuzosin, doxazosin, tamsulosin or terazosin) for moderate to severe LUTS.
- An anticholinergic for overactive bladder symptoms.
- A 5-alpha reductase inhibitor for LUTS and prostate enlargement greater than 30 g or prostate specific antigen greater than 1.4 nanograms/ml, and high risk of progression.
- Combination of alpha blocker and a 5-alpha reductase inhibitor for bothersome moderate to severe LUTS and prostate enlargement greater than 30 g or prostate specific antigen greater than 1.4 nanograms/ml.
- Combination of alpha blocker and an anticholinergic for men with storage symptoms despite treatment with an alpha blocker alone.
- Late afternoon loop diuretic (off-label) for men with nocturnal polyuria.
- Oral desmopressin (off-label) for men with nocturnal polyuria if other medical causes have been excluded and they have not benefited from other treatments.

If LUTS do not respond to conservative management or drug treatment, next steps include discussion of active surveillance (reassurance and lifestyle advice without immediate treatment and with regular follow-up) or active intervention (conservative management or surgical options).

See the NICE pathway on [LUTS in men](#) and the NICE clinical guideline on [LUTS](#) for further details.

Product overview

Drug action

Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). The mean half-life of the drug is 17.5 hours in people who are healthy and steady-state plasma concentrations are attained within 5 days of once-daily dosing. PDE5 is an enzyme found in the corpus cavernosum smooth muscle, as well as in the smooth muscle of the prostate, the bladder and their vascular supply ([Cialis summary of product characteristics](#)).

The exact mechanism by which tadalafil affects symptoms associated with benign prostatic hyperplasia is not known. The [summary of product characteristics](#) for tadalafil describes how inhibition of PDE5 causes relaxation in the vascular supply of the prostate and bladder that increases blood perfusion to these areas, which may be the mechanism by which symptoms of benign prostatic hyperplasia are reduced. These vascular effects may be complemented by inhibition of bladder afferent nerve activity and smooth muscle relaxation of the prostate and bladder.

Newly licensed therapeutic indication

In October 2012, tadalafil (Cialis, 5 mg tablet only, Eli Lilly and Company Ltd) received a European Union marketing authorisation for treating the signs and symptoms of benign prostatic hyperplasia in adult men (Eli Lilly UK: personal communication January 2013).

Previously, in November 2002, tadalafil ([Cialis](#), 2.5 mg, 5 mg, 10 mg and 20 mg tablets, Eli Lilly and Company Ltd) received a European Union marketing authorisation for treating erectile dysfunction in adult men.

The prescribing of tadalafil for erectile dysfunction in England is subject to statutory prescribing restrictions through Schedule 2 of the NHS (general medical services contracts) (prescription of drugs etc.) regulations 2004 and the NHS (Pharmaceutical and Local Pharmaceutical Services) Regulations 2013. The regulations specify in which circumstances prescriptions for certain erectile dysfunction treatments can be reimbursed by the NHS in primary care. Details of the clinical conditions that are covered by the regulations scheme are reproduced in Part XVIIIB of the NHS electronic drug tariff - 'Drugs, medicines and other substances that may be ordered only in certain circumstances'.

These prescribing restrictions do not apply to tadalafil when it is prescribed in primary care on the NHS for benign prostatic hyperplasia (Department of Health: personal communication October 2013).

Course and cost

The [summary of product characteristics](#) for tadalafil advises that the dose of tadalafil for benign prostatic hyperplasia in adult men is 5 mg taken approximately at the same time every day with or without food. This is also the dose for men with both benign prostatic hyperplasia and erectile dysfunction. The efficacy of tadalafil 2.5 mg for treating benign prostatic hyperplasia has not been demonstrated.

When tadalafil is used for treating erectile dysfunction, it can be taken on an as needed basis (10 mg and 20 mg strengths), or as a regular once-daily dose (2.5 mg and 5 mg strengths). To treat benign prostatic hyperplasia, tadalafil should be taken regularly once a day.

A 28-tablet pack of tadalafil 5 mg (Cialis, Eli Lilly and Company Ltd) costs £54.99, representing an annual cost of £716.83 (taken from the [NHS drug tariff](#) February 2013).

Evidence review

This evidence review is based on 2 studies ([Roehrborn et al. 2008](#) and [Donatucci et al. 2011](#)) of tadalafil to treat men with lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia.

[Roehrborn et al. \(2008\)](#) published results from a 12-week, double-blind, placebo-controlled, dose-finding study (2.5 mg, 5 mg, 10 mg and 20 mg daily). After the 12-week, placebo-controlled treatment period, men were given the choice to participate in an open-label extension study (published by [Donatucci et al. 2011](#)) for a period of 1 year, in which all men received tadalafil 5 mg daily.

In addition, 1 systematic review ([Gacci et al. 2012](#)) was identified that looked at the use of phosphodiesterase type 5 (PDE5) inhibitors either alone (7 randomised controlled trials [RCTs], 3214 men) or in combination with alpha blockers (5 RCTs, 216 men) for the treatment of LUTS due to benign prostatic hyperplasia. This combined the results of 4 different PDE5 inhibitors, including but not limited to tadalafil, but did not report efficacy outcomes for tadalafil separately.

Other relevant studies of tadalafil have been published in men with LUTS suggestive of benign prostatic hyperplasia ([Porst et al. 2011](#) and [Oelke et al. 2012](#)), and in men with both erectile dysfunction and LUTS of benign prostatic hyperplasia ([Egerdie et al. 2012](#)). These provide relevant evidence but contained a smaller number of participants randomised to receive tadalafil 5 mg. In addition, the study by [Egerdie et al. \(2012\)](#) focused on treating men with both erectile dysfunction and LUTS of benign prostatic hyperplasia, whereas this evidence summary focuses solely on the treatment of LUTS. The largest study identified using tadalafil 5 mg ([Roehrborn et al. 2008](#)) and the linked longer-term, open-label extension study ([Donatucci et al. 2011](#)) provide the evidence for this summary.

Roehrborn et al. (2008)

- Design: multicentre, double-blind, randomised, placebo-controlled, dose-finding trial with a 12-week treatment period.
- Population: 1058 men, 45 years or older (mean age 62.1 years) with a history of LUTS secondary to benign prostatic hyperplasia of 6 months or longer. Men had to have an International Prostate Symptoms Score (I-PSS) of 13 or more to be included in the study. The I-PSS has 7 symptom questions addressing incomplete bladder emptying, frequency, intermittency, urgency, weak stream, straining and nocturia during the past month. Each question is scored from 0 to 5 with a total score of up to 35 points. Scores range from 0 (asymptomatic) to 35 (very symptomatic) with the following categories of symptom severity: 1–7 mild, 8–19 moderate and 20–35 severe. The I-PSS contains 1 additional question on quality of life due to urinary symptoms, and is assigned a score of 0 to 6, with lower scores indicating a better quality of life. I-PSS total score is a validated tool but it is not clear whether subscores based on clusters of individual questions are also valid.
- Previous treatments: men who received finasteride (within 3 months) or dutasteride (within 12 months) before the placebo run-in period were excluded from the trial. Alpha blockers had been used by 28.8% of men in the trial, and 1.1% had previously used 5-alpha-reductase inhibitors.
- Intervention and comparison: 4-week, treatment-free, wash-out period, followed by a 4-week placebo run-in period, and then a 12-week treatment period with: tadalafil 2.5 mg, 5 mg, 10 mg or 20 mg daily or placebo daily.
- Primary outcome: change in I-PSS from baseline to 12 weeks with tadalafil 5 mg compared with placebo using an intention-to-treat analysis.

- Secondary outcomes included efficacy and dose-response relationship of different doses of tadalafil (assessed using I-PSS total score) and change from baseline to 12-week end point in I-PSS irritative subscore, voiding (obstructive) subscore, I-PSS quality of life, benign prostatic hyperplasia impact index (BPH-II), global assessment question (GAQ), uroflowmetry parameters, and international index of erectile function – erectile function domain (IIEF-EF).

Table 1 Summary of the trial:Roehrborn et al. (2008)

	Tadalafil 5 mg daily	Placebo daily	Analysis
Randomised	n=212	n=211	
ITT	n=212	n=210	Baseline and at least 1 post-baseline measurement available; the excluded patient in the placebo group had been randomised at 2 sites
Completed 12-week treatment	85.9% (182/ 212)	87.3% (185/ 212)	
Baseline I-PSS (±SD)	17.30 (±5.97)	17.08 (±6.36)	No significant difference
Efficacy	n=212	n=210	
Primary outcome: Change in I-PSS ^a , least squares mean (±SE)	-4.87 (±0.49)	-2.27 (±0.49)	p<0.001, absolute difference 2.6 points in favour of tadalafil
Selected secondary outcomes			p values below are for tadalafil (any dose) vs. placebo
Change in I-PSS ^a in patients with mild to moderate LUTS at baseline ^b , least squares mean (±SE)	-4.3 (±4.94)	-1.4 (±6.44)	p<0.001, absolute difference 2.9 points for tadalafil 5 mg vs. placebo
Change in I-PSS ^a in patients with severe LUTS at baseline ^c , least squares mean (±SE)	-6.2 (±6.71)	-3.9 (±5.3)	p<0.05, absolute difference 2.3 points for tadalafil 5 mg vs. placebo

Change in I-PSS irritative subscore ^a , least squares mean (±SE)	-1.89 (±0.23)	-0.99 (±0.23)	p<0.01, absolute difference 0.9 points for tadalafil 5 mg vs. placebo
Change in I-PSS obstructive subscore ^a , least squares mean (±SE)	-2.94 (±0.33)	-1.26 (±0.33)	p<0.001, absolute difference 1.68 points for tadalafil 5 mg vs. placebo
Change in I-PSS quality of life ^a , least squares mean (±SE)	-0.86 (±0.11)	-0.49 (±0.11)	p<0.01, absolute difference 0.37 points for tadalafil 5 mg vs. placebo
Change in maximum urinary flow rate ^a , Qmax, cm/sec, least squares mean (±SE)	1.64 (±0.39)	1.24 (±0.40)	No significant change from baseline compared with placebo (p value not reported)
Safety	n=212	n=211	
Patients reporting 1 or more SAE	0.5% (1/212)	2.8% (6/211)	No statistical test reported
Patients reporting 1 or more AE leading to discontinuation	5.7% (12/212)	2.4% (5/211)	No statistical test reported
Patients reporting 1 or more TEAE	30.7% (65/212)	21.2% (45/211)	No statistical test reported

Notes: The I-PSS irritative subscore sums the scores for: frequency, urgency and nocturia questions. The obstructive subscore sums the scores for: straining, weak stream, incomplete bladder emptying and intermittency questions.

Abbreviations: AE, adverse event; I-PSS, International Prostate Symptoms Score; ITT, intention to treat; LUTS, lower urinary tract symptoms; SAE, serious adverse event; SD, standard deviation; SE, standard error; TEAE, treatment-emergent adverse events.

^a Change from baseline to 12 weeks.

^b n=701, patients had mild to moderate I-PSS scores at baseline across all treatment groups (placebo, 2.5 mg, 5 mg, 10 mg and 20 mg). Patient numbers by treatment group not given.

^c n=352, patients had severe I-PSS scores across all treatment groups (placebo, 2.5 mg, 5 mg, 10 mg and 20 mg). Patient numbers by treatment group not given.

Donatucci et al. (2011)

- Design: 1-year, multicentre, open-label extension study. Safety and efficacy parameters assessed after 1 month and every 3 months thereafter.
- Population: 427 men (from a total of 886 eligible men) who had completed the 12-week, placebo-controlled, dose-finding study (Roehrborn et al. 2008) and elected to take part in the open-label extension phase. Mean age 62.66 years (range 45.57 to 82.20 years). Around a third (32.79%) had previously used alpha blockers, whereas 1.41% had previously used 5-alpha-reductase inhibitors.
- Intervention and comparison: all men used tadalafil 5 mg daily for the duration of the extension study regardless of treatment allocation in the 12-week trial (Roehrborn et al. 2008).
- Concurrent treatments: men agreed not to use any other medical or herbal treatments to treat benign prostate hyperplasia or erectile dysfunction while enrolled in the study.
- Primary outcome was not specified. Selected safety outcomes included: adverse events, changes in vital signs (blood pressure and pulse), clinical laboratory tests (serum chemistry and haematology, urinalysis), prostate specific antigen levels, post-void residual volume and electrocardiograms. Selected efficacy outcomes included: change in I-PSS score, I-PSS subscores, I-PSS quality of life and BPH-II.

Table 2 Summary of the trial: Donatucci et al. (2011)

	Tadalafil 5 mg daily ^a	Analysis
Completed 12-week placebo study	n=886	
Recruited to open-label extension	n=427	48.2% (427/886) of those competing the 12-week trial
Completed year follow-up	70.0% (299/427)	
Secondary efficacy outcomes		No statistical tests reported
Mean change in I-PSS (±SD) week 0 to end point ^b	-5.0 (±6.7)	Scores for 416 participants analysed

Mean change in I-PSS (\pm SD) week 12 to end point ^b	-0.9 (\pm 5.7)	Scores for 416 participants analysed
Mean change in I-PSS irritative subscore (\pm SD) week 0 to end point ^b	-1.9 (\pm 3.0)	Scores for 416 participants analysed
Mean change in I-PSS irritative subscore (\pm SD) week 12 to end point ^b	-0.3 (\pm 2.6)	Scores for 416 participants analysed
Mean change in I-PSS obstructive subscore (\pm SD) week 0 to end point ^b	-3.1 (\pm 4.4)	Scores for 416 participants analysed
Mean change in I-PSS obstructive subscore (\pm SD) week 12 to end point ^b	-0.6 (\pm 3.6)	Scores for 416 participants analysed
Mean change in I-PSS health-related quality of life (\pm SD) week 0 to end point ^b	-1.1 (\pm 1.4)	Scores for 414 participants analysed
Mean change in I-PSS health-related quality of life (\pm SD) week 12 to end point ^b	-0.3 (\pm 1.2)	Scores for 413 participants analysed
Change in maximum urinary flow rate, Qmax, cm/sec (\pm SE)	Not reported	Not reported
Safety		
Patients reporting 1 or more SAE	4.7% (20/427)	No statistical tests reported
Patients reporting 1 or more AE leading to discontinuation	5.2% (22/427)	No statistical tests reported
Patients reporting 1 or more TEAE	57.6% (246/427)	No statistical tests reported

Notes: The I-PSS irritative subscore sums the scores for: frequency, urgency and nocturia. The obstructive subscore sums the scores for: straining, weak stream, incomplete bladder emptying and intermittency.

Abbreviations: AE, adverse event; I-PSS, International Prostate Symptoms Score; SAE, serious adverse events; SD, standard deviation; SE, standard error; TEAE, treatment-emergent adverse events.

^a Tadalafil 5 mg daily from week 12 to week 64. Treatment before this (0–12 weeks) was either placebo or tadalafil at 2.5 mg, 5 mg, 10 mg or 20 mg daily (see [Roehrborn et al. 2008](#)).

^b End point, the last non-missing post-baseline value after visit 7 (week 12).

Clinical effectiveness

In [Roehrborn et al. \(2008\)](#), 5 mg daily dosing of tadalafil statistically significantly improved LUTS compared with placebo. The least squares mean improvement in overall I-PSS was 2.27 points for placebo compared with 4.87 points for tadalafil after 12 weeks of treatment ($p=0.001$). A clinically meaningful improvement in score is defined in the study as a 3-point improvement in I-PSS from baseline. The improvement seen in the study is therefore clinically meaningful with tadalafil but not with placebo. However, the absolute difference between the groups is only 2.6 points, which is not a clinically meaningful difference. Statistically significant improvements in the primary outcome (tadalafil 5 mg compared with placebo) were detected at 4-, 8- and 12-week end points. The statistically significant benefit of tadalafil 5 mg over placebo in improving overall I-PSS at 12 weeks was maintained when the analysis was restricted to men with mild to moderate LUTS or severe LUTS at baseline.

Other statistically significant improvements seen for secondary outcomes at 12 weeks were: I-PSS obstructive subscore, I-PSS irritative subscore, I-PSS quality of life, BPH-II, GAQ and IIEF-EF for doses of 5 mg of tadalafil or greater (except for a non-significant finding for the 10 mg dose for BPH-II compared with placebo, $p=0.056$). No statistically significant improvement was seen for Qmax (peak urinary flow rate) using tadalafil 5 mg compared with placebo (p value not reported).

At baseline assessment, an average of 67.92% of men randomised to receive tadalafil 5 mg had a history of erectile dysfunction. This was numerically similar to the proportions reported in the other treatment arms of the trial. Therefore, the evidence is applicable largely to men with LUTS and erectile dysfunction, but also a proportion of men with LUTS without erectile dysfunction.

The results from [Donatucci et al. \(2011\)](#) indicated that most of the benefit in LUTS associated with tadalafil came within the first 12 weeks of treatment and was maintained or improved to a much smaller degree for up to 1 year. For example, the overall change in total I-PSS in men using tadalafil 5 mg from week 0 to the endpoint (the last non missing post baseline value after visit 7 [week 12]) was a mean of -5.0 points (standard deviation [SD] ± 7.2 points) with a reduction in score indicating an improvement. Between week 12 and the endpoint, scores changed by a mean of $+0.2$ points (SD ± 5.4 points). Considering all participants (those receiving placebo, or tadalafil 2.5 mg, 5 mg, 10 mg or 20 mg, during weeks 0 to 12), I-PSS scores changed by a mean of -5.0 points (SD ± 6.7 points) between week 0 and the endpoint, with a mean change of only -0.9 points (SD ± 5.7 points) seen between week 12 and the endpoint. A similar pattern was observed for the secondary outcomes I-PSS irritative and obstructive subscores.

The meta-analysis by [Gacci et al. \(2012\)](#) found that using PDE5 inhibitors alone (including but not limited to tadalafil, the only PDE5 inhibitor licensed for treating benign prostatic hyperplasia with LUTS) improved LUTS (mean change in I-PSS -2.8 points from baseline to end of study, $p < 0.0001$) and erectile function (mean change in International Index of Erectile Function [IIEF] score from baseline to end of study +5.5, $p < 0.0001$) compared with placebo but not maximum urinary flow rate. This meta-analysis compared the results of 2250 men (83.5%, 1879 completed the studies) using PDE5 inhibitors alone, with 964 men (90.2%, 870 completed the studies) using placebo. When used in combination with alpha blockers (109 men, 103 [94.5%] completed the studies), PDE5 inhibitors improved LUTS (I-PSS -1.8, $p = 0.05$), erectile dysfunction (IIEF +3.6, $p < 0.0001$) and maximum urinary flow rate (Q_{max} +1.5 ml/s, $p < 0.0001$) compared with alpha blockers alone (107 men, 99 [92.5%] completed the studies).

Safety

Statistical analysis of safety data from [Roehrborn et al. \(2008\)](#) and the year-long extension study by [Donatucci et al. \(2011\)](#) was absent, limiting the conclusion that can be drawn.

In [Roehrborn et al. \(2008\)](#), relatively few men using tadalafil 5 mg daily reported 1 or more severe adverse events (1 out of 212 men, 0.5%) and adverse events leading to discontinuation (12 out of 212 men, 5.7%), whereas 65 out of 212 men (30.7%) reported 1 or more treatment-emergent adverse events of any severity.

During the 1-year [open-label extension study](#) (assessing 427 men), 20 men (4.7%) reported severe adverse events, 22 men (5.2%) reported adverse events leading to discontinuation, and 246 men (57.6%) reported 1 or more treatment-emergent adverse events of any severity.

The most commonly reported treatment-emergent adverse events were: dyspepsia (4%), gastro-oesophageal reflux disease (4.0%), back pain (3.7%), headache (3.0%), sinusitis (2.8%), hypertension (2.6%), and cough (2.1%).

Of the 246 men (57.6%) in the extension study reporting at least 1 treatment-emergent adverse event, most were classed as mild (44%) or moderate (45%) in severity.

Of the 20 men (4.7%) who reported at least 1 serious adverse event, 2 were considered to have serious adverse events possibly related to tadalafil: 1 man had worsening of coronary heart disease and 1 experienced global amnesia.

A meta-analysis of adverse events included in [Gacci et al. \(2012\)](#) reported a higher risk of flushing, gastro-oesophageal reflux, headache and dyspepsia after using PDE5 inhibitors alone (including but not limited to tadalafil) compared with placebo.

The full list of cautions, contraindications and side effects derived from all the clinical trials available when tadalafil was licensed are described in the [summary of product characteristics](#). Of note, tadalafil is contraindicated in patients receiving nitrates; in patients with cardiac disease for whom sexual activity is inadvisable; and in patients with non-arteritic ischaemic optic neuropathy leading to loss of vision, uncontrolled arrhythmias, hypotension, uncontrolled hypertension, recent stroke, unstable angina, recent myocardial infarction or recent New York Heart Association class 2 or greater heart failure.

Evidence strengths and limitations

[Roehrborn et al. \(2008\)](#) had relatively high completion rates (85.9% in those using tadalafil 5 mg compared with 87.3% using placebo) after 12 weeks of treatment and was well powered to detect differences between tadalafil 5 mg and placebo treatments, suggesting that the results are reliable. A further strength is that longer-term safety and efficacy results (up to a year) were also published for those using tadalafil 5 mg daily ([Donatucci et al. 2011](#)); though the completion rates for this study were lower (69.9%).

I-PSS total score is a validated tool for assessing LUTS but it is not clear whether the subscores used in the studies (based on clusters of individual questions) are equally valid. Therefore, interpretation of these subscores should be more cautious.

Alpha blockers had been used previously in only 27.83% of men assigned tadalafil 5 mg in the 12-week, double-blind study by [Roehrborn et al. \(2008\)](#); therefore, the evidence is mainly applicable to tadalafil used as a first-line treatment for LUTS associated with benign prostatic hyperplasia. It is not clear whether tadalafil would lead to equivalent significant improvements in LUTS symptoms compared with placebo if the results were restricted only to those who had already used alpha blockers (that is, if tadalafil was used as a second-line treatment). Only 48.2% of eligible men self-selected to participate in the extension study after the initial 12-week treatment. This may have led to selection bias in the extension trial by including only men most responsive and/or tolerant to the drug during the initial 12-week trial. If this was the case, it could lead to an overestimate in the year-long efficacy of tadalafil and an underestimate in the prevalence of adverse events.

The lack of statistical analysis limits the interpretation of the safety and tolerability data from both studies.

Owing to the scope of this evidence summary, the summary focused on the results of only 2 study publications ([Roehrborn et al. 2008](#) and [Donatucci et al. 2011](#)). [Roehrborn et al. \(2008\)](#) and the linked longer-term open-label extension study, [Donatucci et al. \(2011\)](#), were selected because together, they have reported outcomes from 1058 men initially randomised in 92 centres across 10 countries. As such, [Roehrborn et al. \(2008\)](#) was identified as the RCT with the largest group of men receiving tadalafil 5 mg (the dose of interest), and the open-label extension by [Donatucci et al. \(2011\)](#) provided the longest follow-up (1 year). Additional published studies also contribute to the evidence base on efficacy or safety, and were reviewed by the European Medicines Agency before issuing a marketing authorisation. These were not reviewed in this evidence summary.

Context

Treatment alternatives

The NICE clinical guideline on [lower urinary tract symptoms \(LUTS\)](#) recommends using alpha blockers to treat men with bothersome moderate to severe LUTS, including, but not specific to, LUTS secondary to benign prostatic hyperplasia. The alpha blockers include:

- Alfuzosin 2.5 mg 3 times daily, maximum 10 mg daily. Older people (aged over 65 years) should initially take 2.5 mg twice daily.
- Doxazosin initially 1 mg daily; dose may be doubled at intervals of 1 to 2 weeks according to response, up to a maximum of 8 mg daily; usual maintenance 2 to 4 mg daily.
- Tamsulosin 400 micrograms daily.
- Terazosin initially 1 mg at bedtime; if necessary, dose may be doubled at intervals of 1 to 2 weeks according to response, up to a maximum of 10 mg once daily; usual maintenance 5 to 10 mg daily.

For men with LUTS and an enlarged prostate (larger than 30 g) or a prostate specific antigen level greater than 1.4 nanograms/ml, the NICE clinical guideline on [LUTS](#) recommends 5-alpha reductase inhibitors. The 5-alpha reductase inhibitors include:

- Dutasteride 500 micrograms daily.
- Finasteride 5 mg daily.

Dosing information comes from the [British national formulary](#).

The [introduction](#) in this evidence summary gives further details on the use of different drug therapies for LUTS. For full details, see the NICE clinical guideline on [LUTS](#).

[Donatucci et al. \(2011\)](#) describes how these standard drug therapies may be effective at reducing LUTS and improving urinary flow rates but are associated with commonly reported side effects. For alpha blockers, these include orthostatic hypotension, dizziness, asthenia (weakness), ejaculatory problems and nasal congestion. For 5-alpha reductase inhibitors, they include decreased libido, ejaculatory dysfunction and erectile dysfunction. Drugs with fewer or less severe side effects have been tested, including phosphodiesterase type 5 inhibitors used in the treatment of erectile dysfunction, such as tadalafil.

Costs of treatment alternatives

The main drug treatments that NICE has recommended for LUTS associated with benign prostatic hyperplasia are alpha blockers and 5-alpha reductase inhibitors. Table 3 shows approximate annual costs of alpha blockers and 5-alpha reductase inhibitors compared with tadalafil.

Table 3 Costs of treatment alternatives

Drug	Usual dosage ^a	Annual cost ^{b,c}
Tadalafil tablets	1×5 mg once daily	£716.83
Alfuzosin tablets	1×2.5 mg 3 times daily	£122.28
Doxazosin tablets	1×2 mg once daily to 1×4 mg once daily	£10.95 to £15.25
Tamsulosin capsules	1×400 micrograms once daily	£65.33
Terazosin tablets	1×5 mg to 1×10 mg once daily	£32.72 to £97.12
Dutasteride capsules	1×500 micrograms once daily	£362.20
Finasteride tablets	1×5 mg once daily	£22.03

^a The doses shown are usual doses taken from the relevant [summary of product characteristics](#) or [British National Formulary](#) but do not represent the full range that can be used and do not imply therapeutic equivalence.

^b All costs are taken from the [Drug Tariff](#), March 2013.

^c Costs stated are for the simplest regimen, for example 1×10 mg tablet, but in some instances it may be more cost effective to prescribe the dose as 2×5 mg. See the [drug tariff](#) for a list of available strengths and costs.

Estimated impact for the NHS

Likely place in therapy

Tadalafil (5 mg only) represents an additional drug option for treating lower urinary tract symptoms (LUTS) caused by benign prostatic hyperplasia, and is the only drug in its class licensed for this. Assessing its likely place in therapy in relation to current drug therapies is difficult because there are few published randomised trials of first-line, second-line or combination therapies (tadalafil plus another drug) compared with current best practice.

The 2 studies ([Roehrborn et al. 2008](#) and [Donatucci et al. 2011](#)) in this evidence summary used tadalafil as either a first- or second-line (after alpha blockers) monotherapy. Trials have also been undertaken of tadalafil in combination with alpha blockers; for example, 2 randomised controlled trials were identified in [Gacci et al. \(2012\)](#). However, the total number of men in the combination arm who completed the study is too small (34 men) to draw valid conclusions.

When making decisions about the use of tadalafil, localities will need to take this evidence of marginal clinical effectiveness into account alongside the one year data on tolerability. The lack of studies comparing tadalafil alone with an active comparator further limits the usefulness of these data. The acquisition cost of tadalafil is also higher than other treatment options.

The prescribing of tadalafil for erectile dysfunction in England is subject to statutory prescribing restrictions through Schedule 2 of the NHS (general medical services contracts) (prescription of drugs etc.) regulations 2004 and the NHS (Pharmaceutical and Local Pharmaceutical Services) Regulations 2013. These prescribing restrictions do not apply to tadalafil when it is prescribed in primary care on the NHS for benign prostatic hyperplasia (Department of Health: personal communication October 2013).

Estimated usage

It is not possible to provide estimated usage based on the available data.

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Changes after publication

October 2013: The [Key points from the evidence](#), [Newly licensed therapeutic indication](#) and [Likely place in therapy](#) sections have been updated in response to personal communication from the Department of Health.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance**.

For information about the process used to develop this evidence summary, see [Evidence summaries: new medicines – interim process statement](#).

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