New Medicine Assessment
Tadalafil 2.5 mg & 5 mg (Cialis®)
For Erectile Dysfunction

Recommendation:

Prescribing within specialist Sexual Health Service - Red

Tadalafil 2.5 mg and 5 mg once daily tablets are recommended for prescribing in Lancashire only when provided by a specialist Sexual Health Service as treatment for erectile dysfunction in the following circumstances:

- where performance anxiety is significant **and/or**
- to support masturbatory/behavioural programs, whereby the erection would require additional support to enable the program to be successful.

Rationale: Use in these circumstances will be for a clearly defined cohort of patients who will receive a discrete programme of treatment by specialists under a Sexual Health service.

Prescribing within Primary Care - Black

Outside of the group of patients and circumstances defined by the LMMG where treatment is provided by a specialist Sexual Health service, tadalafil 2.5 mg and 5 mg once daily tablets are not recommended for prescribing in Lancashire for the treatment of erectile dysfunction:

- where up to and including twice weekly dosing of on demand tadalafil is required **or**
- where more than twice weekly dosing of on demand tadalafil is required

Rationale: No significant clinical or financial advantage has been demonstrated when daily tadalafil is prescribed for patients requiring on demand tadalafil up to and including twice a week. Additionally, use of a daily preparation of tadalafil when treatment is needed twice weekly or less may unnecessarily expose patients to the drug on a continual, long term basis.

Research shows that the average frequency of sexual intercourse in the 40–60 age range is once a week.[1] The Department of Health advises that:

'One treatment per week will be appropriate for most patients being treated for erectile dysfunction. If the GP in exercising his clinical judgement considers that more than one treatment a week is appropriate they should prescribe that amount on the NHS'[1, 2]

Treatment of erectile dysfunction more than twice weekly is significantly outside Department of Health general prescribing guidance. Prescribing a daily drug for erectile dysfunction may lead to stockpiling or diversion.

Summary of supporting evidence:

Erectile dysfunction (ED) is very common, with one study indicating an overall prevalence of 52% in non-institutionalised men between the ages of 40 and 70.

Many of the ED guidelines give the option of low dose tadalafil once daily as an alternative to on demand phosphodiesterase type 5 inhibitor (PDE5i) treatment in couples who anticipate sexual activity at least twice a week

In studies involving almost 2000 men with erectile dysfunction, tadalafil once daily tablets demonstrated a clinically important improvement in erectile function when compared to placebo; IIEF-EF improved by 4.2 and 5.4 for 2.5mg and 5mg tadalafil respectively. A difference of ≥4 is considered clinically important. Answers to the SEP3 question (relating to sustaining erection long enough for successful intercourse) also indicated significantly improved erectile function for tadalafil compared to placebo.

A 2014 study with a cohort of 623 adult men found that treatment with tadalafil 2.5-5mg and 5mg once daily both resulted in a statistically significant higher percentage of patients with an IIEF-EF domain score in the normal range than placebo.

Tadalafil has a well-established safety profile from on demand use at higher doses. The once daily studies did not indicate anything unexpected or raise any additional safety concerns.

Tadalafil once daily is significantly more expensive than generic sildenafil. On demand tadalafil taken twice a week is approximately the same price as once daily tadalafil.

Details of Review

Name of medicine (generic & brand name): Tadalafil (Cialis®)

Strength(s) and form(s): 2.5 mg and 5 mg Tablets[3]

Dose and administration: 5 mg once daily, reduced to 2.5 mg once daily according to response

BNF therapeutic class / mode of action: Chapter 7.4.5 Drugs for erectile dysfunction: Phosphodiesterase type-5 inhibitors (PDE-5 inhibitors)

Licensed indication(s): Benign prostatic hyperplasia; erectile dysfunction; pulmonary hypertension.[3]

Proposed use (if different from, or in addition to, licensed indication above): To be used for erectile dysfunction in cases: - where frequent, more than twice weekly dosing is required, **or**   - where performance anxiety is significant, **or**   - to support masturbatory/behavioural programs, whereby the erection would require additional support to enable the program to be successful.   If the issues are purely psychogenic, the aim is that following therapy the client will no longer require medication and if medication is required, the discharge letter provides information on the options for continued prescribing. Clients are educated about cost and the requirement for them to receive private prescriptions.   **Please note: this is the wording as per the drug request received from specialists, please refer to the recommendation (page 1) for the agreed place in therapy.**

Course and cost: 2.5 mg and 5 mg both £54.99 for 28 tablets. This equates to an annual cost per patient of £716.84[4] if taken for a whole year.

Current standard of care/comparator therapies: First line is generic Sildenafil 50 mg tablets on demand (dose can be increased up to 100 mg or reduced to 25 mg if required). Second line is tadalafil 10 mg on demand (increased to 20 mg if needed).[5] Non-PDE-5 inhibitor alternatives include vacuum pumps and alprostadil formulations.

Relevant NICE guidance: No NICE guidance relating directly to tadalafil use in erectile dysfunction, although there is NICE ESNM erectile dysfunction advice for both avanafil[6] and alprostadil.[7] In addition there is an erectile dysfunction NICE clinical knowledge summary.[8]   Other relevant guidance includes the All Wales Medicines Strategy Group guidance on prescribing for Erectile Dysfunction[9], the European association of Urology guidelines on male sexual dysfunction[10] and the British Society for Sexual Medicine guidelines on the management of erectile dysfunction.[11]

Disease Background

Erectile Dysfunction (ED), previously known as impotence, is defined by the 2015 European Association of Urology (EAU) guidelines[10] as the persistent inability to get and maintain an erection that is sufficient to permit satisfactory sexual performance. It is a very common condition, an overall prevalence of 52% ED in non-institutionalised men between the ages of 40 and 70 was reported in the Massachusetts Male Aging Study.[10] ED can have a significant impact on quality of life of both patients and their partners.[8, 10-12] ED is often being a symptom of other underlying, treatable conditions, risk factors including cardiovascular disease, diabetes, hyperlipidaemia and major surgery (e.g. radical prostatectomy)[10] and men with mild ED should be evaluated for these risks.

Many of the studies identified in this new medicines review used the International Index of Erectile Function erectile function (IIEF-EF) domain score as a primary outcome. The IIEF-EF is a validated questionnaire which the patient completes in order to give a measure of erectile function. The lower the score, the worse the dysfunction,[13] e.g. 6-10 for severe dysfunction, through to 26-30 for no dysfunction. A difference of at least 4 points in the erectile function domain is considered clinically important.[14] Another frequently used measure is the mean per-patient percentage of yes response to the Sexual Encounter Profile questions 2 - were you able to insert your penis into partner's vagina? and 3 - did your erection last long enough for you to have successful intercourse?

The EAU guidelines state that the primary goal in the management strategy of a patient with ED is to determine the cause, and treat it when possible.[10] Lifestyle changes and risk factor modification must precede or accompany any pharmacological treatment. ED can be treated successfully, but can only be cured in limited circumstances: e.g. some hormonal causes can be aided by testosterone replacement therapy. Most men with ED will be treated with therapeutic options that are not cause specific, allowing a structured treatment strategy to be adopted.[8, 12] After lifestyle changes and risk factor modification, the guidelines recommend first-line therapy with one of three licensed phosphodiesterase type 5 inhibitor (PDE5i) medications; sildenafil, tadalafil or vardenafil. The choice of drug is dependent upon the frequency of intercourse and the patient's personal experience.

PDE5is do not initiate erections, and sexual stimulation is required to enable an erection.[10] Sildenafil was the first PDE5i available and is now available as a generic. Tadalafil's patent expires in November 2017 and vardenafil's expires in October 2018. Sildenafil is effective 30-60 minutes after administration, with efficacy reduced after heavy, fatty meals.[10] The effect may be maintained for up to 12 hours and studies have reported improved erections in 56-84% of men taking sildenafil (dependent upon dose) compared to 25% of men taking placebo.[10] Its efficacy has been successfully established in almost every subgroup of patients with ED.[10] Tadalafil is effective from 30 minutes post administration, it has a maximum efficacy at around 2 hours, a maintenance of efficacy for up to 36 hours and is not affected by food.[10] When taken on demand before anticipated sexual activity, tadalafil has been shown to provide improved erections in 67% and 81% of a general ED population taking 10 and 20 mg tadalafil respectively, compared to 35% of men taking placebo.[10]

The British Society for Sexual Medicine has produced guidelines on the management of erectile dysfunction.[11] In line with the European guidelines, the British guidelines recommend addressing lifestyle and other possible causes of ED alongside specific pharmacotherapy.[11] They also recommend the same first and second-line treatment pathways. When referring to once-a-day therapy, the British guidance informs that where sexual activity is anticipated more than twice a week, once-daily dosing may be a more cost-effective option than on-demand treatment. In addition, the British guidelines report that clinical trials suggest a marked reduction in reported

adverse effects to on-demand treatment, but there is no reference provided to support this statement.[11]

Tadalafil on demand

Tadalafil was first licensed as an 'on demand' treatment of erectile dysfunction, the recommended dose being 10 mg taken prior to anticipated sexual activity with or without food.[15] If 10 mg does not produce an adequate effect, 20 mg might be tried. It may be taken at least 30 minutes prior to sexual activity. The maximum dose frequency is once per day. The SPC of tadalafil (Cialis®) states:

> In a 12-week study performed in 186 patients (142 tadalafil, 44 placebo) with erectile dysfunction secondary to spinal cord injury, tadalafil significantly improved the erectile function leading to a mean per-subject proportion of successful attempts in patients treated with tadalafil 10 or 20 mg (flexible-dose, on demand) of 48% as compared to 17% with placebo.

and

> Tadalafil at doses of 2 to 100mg has been evaluated in 16 clinical studies involving 3250 patients, including patients with erectile dysfunction of various severities (mild, moderate, severe), etiologies, ages (range 21-86 years), and ethnicities. Most patients reported erectile dysfunction of at least 1 year in duration. In the primary efficacy studies of general populations, 81% of patients reported that tadalafil improved their erections as compared to 35% with placebo. Also, patients with erectile dysfunction in all severity categories reported improved erections whilst taking tadalafil (86%, 83%, and 72% for mild, moderate, and severe, respectively, as compared to 45%, 42%, and 19% with placebo). In the primary efficacy studies, 75% of intercourse attempts were successful in tadalafil-treated patients as compared to 32% with placebo.[15]

Tadalafil daily

A low dose tadalafil formulation for daily use has been approved by the European Medicines Agency (EMA); it is the focus of this review. The SPC of tadalafil (Cialis®) states:

> For once-a-day evaluation of tadalafil at doses of 2.5, 5, and 10 mg 3 clinical studies were initially conducted involving 853 patients of various ages (range 21-82 years) and ethnicities, with erectile dysfunction of various severities (mild, moderate, severe) and etiologies. In the two primary efficacy studies of general populations, the mean per-subject proportion of successful intercourse attempts were 57 and 67% on tadalafil 5mg, 50% on tadalafil 2.5mg as compared to 31 and 37% with placebo. In the study in patients with erectile dysfunction secondary to diabetes, the mean per-subject proportion of successful attempts were 41 and 46% on tadalafil 5mg and 2.5mg, respectively, as compared to 28% with placebo. Most patients in these three studies were responders to previous on-demand treatment with PDE5 inhibitors. In a subsequent study, 217 patients who were treatment-naive to PDE5 inhibitors were randomised to tadalafil 5mg once a day vs. placebo. The mean per-subject proportion of successful sexual intercourse attempts was 68% for tadalafil patients compared to 52% for patients on placebo. Daily dosing of tadalafil has been shown to be well tolerated and significantly improves erectile function.

It concludes stating that tadalafil 5 mg once-a-day provides an alternative to on-demand dosing of tadalafil for couples who prefer spontaneous rather than scheduled sexual activities or who anticipate frequent sexual activity.[10]

This is in line with the EMA, who recommend that for patients who anticipate a frequent use of tadalafil (i.e. at least twice weekly) a once-a-day regimen with tadalafil 2.5 mg or 5 mg might be considered suitable, based on patient choice and physicians judgement.[10]

The All Wales Medicines Strategy Group produced guidance on prescribing for ED in 2012; in relation to once-daily preparations, their recommendation was that they should only be

considered in patients who anticipate frequent use of single dose preparations (i.e. at least twice-weekly) and that it should be based on the clinician's judgement.[9]

The SMC has accepted tadalafil 2.5mg and 5 mg once-a-day for use in NHS Scotland for regular once-daily administration in patients with erectile dysfunction responding to an on-demand regimen of tadalafil who anticipate frequent use (at least twice weekly). Compared with on-demand use of tadalafil, the low dose regular regimen is expected to be cost-neutral.[16]

Tadalafil is an alternative to sildenafil, listed as second line in LMMG guidelines for the management of erectile dysfunction.[5] It is subject to the same NHS prescribing restrictions as other treatments for ED.

PDE5i treatments for ED, with the exception of generic sildenafil, are only available at NHS expense for men with prostate cancer, kidney failure treated with dialysis or transplantation, spinal cord injury, diabetes, multiple sclerosis, single gene neurological disease, spina bifida, Parkinson's disease, polio or severe pelvic injury, men who have undergone radical pelvic surgery or prostatectomy and for men who were already receiving drug treatment for impotence on the NHS on 14 September 1998. Prescriptions must be endorsed with "SLS".[17]

This review will assesses the evidence relating to the use of once-daily tadalafil, and make a recommendation as to whether or not its use in the management of ED can be supported within Lancashire.

Summary of evidence

Summary of efficacy data in proposed use:

The majority of evidence for the use of tadalafil 2.5 or 5 mg once-a-day used in men with ED is pooled and analysed in Porst et al 2014[18] which forms the basis of this evidence review. Additional papers which were either were not included or have been published more recently are discussed separately below.

Six randomised, double-blind, placebo-controlled, clinical studies were pooled and discussed in Porst et al.[18] The studies included 1913 men aged at least 18 years with ≥ 3 months duration of erectile dysfunction and were published between 2006 and 2012 (Porst et al 2006[19], Rajfer et al 2007,[20] Hatzichristou et al 2008,[21] Rubio-Aurioles et al 2009,[22] Montorsi et al 2011[23] and Egerdie et al 2012[24]). The pooled analysis, whilst including many of the major trials found in this area, has the caveat of being designed, conducted and supported by Eli Lilly, the manufacturer of Cialis®.[18]

Patients were randomly assigned to take placebo (n=596), 2.5 mg (n=394) or 5 mg tadalafil (n=923) once-a-day at the same time each day. Patients completed the Sexual Encounter Profile (SEP) after each sexual intercourse attempt and the IIEF at baseline and at 4 week intervals for the duration of treatment.[18]

Tadalafil treatment in the overall population significantly improved erectile function compared to placebo as measured by IIEF-EF (4.2, 95% CI 3.3-5.1 and 5.4 95% CI 4.7-6.1 for 2.5 and 5mg respectively) and SEP3 improvements (17.8 95% CI 13.6-22.0 and 23.6 95% CI 20.2-26.9 respectively). The improvements for tadalafil 5 mg were significantly greater compared with 2.5 mg for SEP 3 (p=0.007) IIEF-EF score (p=0.008) and IIEF-EF normalization (p=0.036). The paper concluded that tadalafil 2.5 and 5 mg once-a-day were effective in improving erectile function. In the overall population, the IIEF-EF improvement of placebo-treated patients (1.7) did not reach the overall Minimal Clinically Important Difference criterion of ≥4 points.[18]

EMEA and Licensing Studies

The license extension from on demand dosing to daily dosing was granted based on evidence from 3 of the phase III randomised, double-blind, placebo controlled, parallel design multicentre studies[19-21] which were included in the analysis by Porst, above. The three studies used the same three co-primary efficacy variables of IIEF-EF and SEP2 and 3[25], they were all of similar design

with a 4-week treatment-free run in followed by a placebo-controlled double-blind treatment period of 12 or 24 weeks and two studies also had an open-label extension.

The demographics and baseline characteristics of the study populations were similar, except all subjects in study LVFZ[21] had diabetes mellitus.[25] The EPAR for the once daily regimen notes that all three studies were similar to the pivotal studies performed to support as-needed dosing. It went on to state the results from studies LVCV[20] and LVFP[19] showed a statistically significant improvement for each of the co-primary endpoints in patients treated with all doses of tadalafil compared to placebo.[25] In LVCV[20] tadalafil 5 mg once-a-day showed similar results to tadalafil 10 mg as-needed dosing whereas in LVFP19 the efficacy of once-a-day 5 mg tadalafil was similar to that of tadalafil 20 mg as-needed dosing. The patients with diabetes studied in LVFZ[21] showed a lower magnitude of change for each of the co-primary endpoints compared to the as-needed regimen, and successful intercourse as indicated by a "yes" response to SEP3 question were 41-46%.[25]

Efficacy results from pivotal licensing studies (from London New Drugs Group Primary Care Briefing[26])

		IIEF-EF mean baseline (range)	IIEF-EF mean endpoint‡	SEP 2 'Yes' at baseline	SEP 2 'Yes' at endpoint	SEP 3 'Yes' at baseline	SEP 3 'Yes' at endpoint
Porst et al	Placebo (n=54)	14.1 (1-29)	15.0	Not stated	51.7%	Not stated	36.7%
	5mg (n=109)	13.1 (3-29)	22.8*	"	79.4%*	"	67.2%*
	10mg (n=105)§	13.4 (4-29)	22.8*	"	81.2%*	"	72.8%*
Hatzichristou et al	Placebo (n-=100)	13.5 (3-27)	14.7	37.7%	43.0%	20.1%	28.2%
	Tadalafil 2.5mg (n=100)	13.5 (5-29)	18.3†	41.8%	62.3%†	20.1%	46.0%†
	Tadalafil 5mg (n=98)	12.6 (1-28)	17.2†	32.2%	61.1%†	16.1%	41.1%†
Rajfer et al	Placebo (n=94)	13.4 (3-28)	14.6	45.9%	51.1%	21.8%	31.3%
	Tadalafil 2.5mg (n=96)	13.1 (1-28)	19.1*	41%	65.3%*	18.8%	50.0%*
	Tadalafil 5mg (n=97)	13.8 (5-28)	20.8*	44.5%	70.7%*	21.8%	56.9%*

* p<0.001
† p≤0.005
‡ Changes of ≥4 in the IIEF-EF are considered clinically meaningful, 1-10 = severe, 11-16 = moderate, 17-5 = mild, ≥26 = none[7]
§ 10mg not licensed for daily use.

The EPAR discusses the lack of direct head to head comparative studies between once daily and as required dosing of tadalafil. It conducted an analysis of existing as required dosing data and compared this to the pivotal study data for once daily dosing and concluded that the clinical effects were similar. It also concluded that the clinical data supported some evidence that the once-a day regimen might be a suitable alternative for the subset of patients with ED with frequent sexual intercourse attempts (e.g. at least twice weekly) for a limited period and according to the treating physician's judgement and patient convenience.25 It went on to state that this dosage regimen would only apply to this restricted population, as the once-a-day treatment could represent excessive dosing for men with ED who have infrequent need for medication to facilitate sexual activity.[25]

Extension Study

Open label extension studies of one-year (study LVCV(N = 234)) or 2-year (study LVFP (N = 238)) were conducted to assess safety and efficacy when the tadalafil 5mg was used for extended periods.[27] Mean IIEF EF domain scores improved from baseline to the conclusions of the 1- and 2-year open-label extensions, respectively: +10.4 and +10.8. At the conclusion of the 2-year open-label extension, 95.7% and 92.1% of the patients reported positive responses to GAQ1 (has the treatment improved your erections) and GAQ2 (if yes to GAQ 1, has the treatment improved your ability to engage in sexual activity), respectively.

Additional Studies

The following trials were not included in the EPAR or either of the papers discussed above. Kim et al[28] conducted a randomised, double-blind, placebo-controlled study with a cohort of 623 adult

patients suffering from ED for a duration of at least 3 months. Full details can be found in the table in Appendix A. Treatment with tadalafil 2.5 to 5 mg and 5 mg both resulted in a statistically significant higher percentage of patients with an IIEF-EF domain score in the normal range (≥26) It concluded that treatment with tadalafil once-a-day significantly improved erectile function in men with mild to mild-moderate impairments in erectile function following PRN PDE5 inhibitor treatment, with approximately 40% of these men able to achieve normal erectile function when treated with tadalafil once-a-day.[28] Buvat et al 2014[29] was an observational study and thus was not blinded; however it does include a large cohort of patients (n=975) and compares the once-a-day dosing of tadalafil with the active comparator of PRN PDE5i use. The primary outcome was time to discontinuation; of the 773 patients who were prescribed and took tadalafil once-a-day, 107 had discontinuation events during the 6-month observation. Kaplan–Meier estimates for continuing on once daily tadalafil were 94.0% (95%CI 92.3, 95.7), 88.3% (85.9, 90.6) and 86.3% (83.7, 88.9) of patients still adhered to tadalafil once-a-day at 2, 4 and 6 months respectively. The most frequently reported AE was headache (10 patients; 1.3%); no new/unexpected safety signals were observed.[29]

Summary of safety data:

The SPC for tadalafil (Cialis®)[15] list the same adverse events and adverse event frequencies for the on demand and once daily presentations of the drug, collated from clinical studies and postmarketing reports:

Common (≥1/100 to <1/10) – headache, flushing, nasal congestion, dyspepsia, gastro-oesophageal reflux, back pain, myalgia, pain in extremity

Uncommon (≥1/1,000 to <1/100) - Hypersensitivity reactions, dizziness, blurred vision, Sensations described as eye pain, tinnitus, tachycardia, palpitations, hypotension, hypertension, dyspnoea, epistaxis, abdominal pain, rash, hyperhydrosis (sweating), haematuria, penile haemorrhage, haematospermia, chest pain

Rare (≥1/10,000 to <1/1,000) – Angioedema, stroke (including haemorrhagic events), syncope, transient ischaemic attacks, migraine, seizures, transient amnesia, visual field defect, swelling of eyelids, conjunctival hyperaemia, non-arteritic anterior ischaemic optic neuropathy, retinal vascular occlusion, sudden hearing loss, myocardial infarction, unstable angina pectoris, ventricular arrhythmia, urticaria, Stevens-Johnson syndrome, exfoliative dermatitis, prolonged erections, priapism, facial oedema, sudden cardiac death

The EPAR states:[25] The incidence of treatment-emergent adverse events was similar between the tadalafil 5 mg and 2.5 mg once-a-day dosing groups (2.5 mg, 47.4%; 5 mg, 50.0%), and lower for the placebo group (36.3%). The incidence of serious adverse events, however, was similar between tadalafil- and placebo-treated subjects. The incidence of treatment-emergent adverse events in the 19-study integrated database for tadalafil as-needed dosing (10 mg, 46.2%; 20 mg, 47.5%) was similar to the incidence of treatment-emergent adverse events observed for tadalafil 5 mg and 2.5 mg once-a-day dosing. In the 1-year, long-term, open-label extension periods, when all subjects received tadalafil 5 mg once a-day dosing, the overall incidence of treatment-emergent adverse events was 57.2%. This incidence was lower than the incidence of treatment-emergent adverse events during the first year of the open label, tadalafil as-needed comparator study (65.3%). Overall, the proportion of patients experiencing SAEs in the 12-week placebo-controlled once-a-day studies was 2.0 % in placebo, 1.5% in tadalafil 2.5mg, and 1.6% in tadalafil 5mg groups as compared to 1%, 0.7% and 1.2% in placebo, tadalafil 10mg and tadalafil 20mg 'as-needed' dosing.[25]

In the open label extension studies of the pivotal trials[27] overall, 208/234 (88.9%) and 139/238 (58.4%) patients completed the 1 and 2 year studies, respectively. No study drug-related serious adverse events were observed. Treatment-emergent adverse events observed in 5% of the patients during the first year of either open-label extension were dyspepsia, headache, back pain, and influenza. One hundred twenty-five of 234 (53.4%) patients experienced a TEAE during the

1-year open-label extension, and 171/238 (71.8%) patients experienced a TEAE during the 2-year open-label extension, with 150/171 (87.7%) experiencing the TEAE(s) during the first year. No clinically meaningful abnormalities associated with tadalafil were observed for electrocardiograms or clinical laboratory measures.

The analysis in Porst et al 2014[18] reports that 119 of 596 (19.97%) placebo patients experienced treatment emergent adverse events (TEAEs) that were reported by ≥2% of patients across the three treatment groups. This compares to 111 of 394 (28.17%) patients taking tadalafil 2.5 mg once daily and 222 of 923 (24.05%) patients taking tadalafil 5 mg once daily. The most frequently reported TEAEs across the 6 studies were headache, nasopharyngitis, back pain/myalgia, dyspepsia and influenza; the paper reports this is consistent with the known safety profile for tadalafil and that no unexpected safety findings were identified.

Kim et al[28] found that nasal congestion was the only AE leading to discontinuation reported by more than one subject (2 in the 2.5mg-5mg group). It went on to state that occurrence of AEs leading to discontinuation were not significantly different in the treatment groups compared to placebo. Tadalafil was shown to have an adverse event profile generally in line with the SPC, the frequency of adverse events being greater with 5mg compared to 2.5mg tadalafil.

Strengths and limitations of the evidence:

Strengths:

- There are several double-blind, randomised controlled trials with sufficient numbers to be adequately powered.

- The patient group of adult males with diagnosed ED of at least 3 months duration is appropriate.

- The interventions of either 2.5 mg, 2.5 to 5 mg or 5 mg are all relevant to the licensed preparation.

- The most frequently used primary outcome measures in the majority of studies were differences from baseline in IIEF-EF and "yes" responses to SEP2 and SEP3. These were appropriate and the questions answered in these surveys were patient orientated outcomes relevant to patients suffering from ED.

Limitations:

- There is a potential for bias in the pooled analysis from Porst et al. 2014[18] as the drug's manufacturers were involved in the production of the journal article.

- Porst et al. 2006[19], which was also included in the EPAR, included a cohort of patients receiving 10 mg once daily which is not a licensed dose.

- There are no head to head randomised double-blind studies of daily versus on demand tadalafil therefore assumptions of equivalent efficacy are necessary when comparing the two presentations of the drug.

Summary of evidence on cost effectiveness:

No published evidence on the cost-effectiveness of tadalafil 2.5 mg and/or 5 mg daily in the UK has been identified.

Prescribing and risk management issues:

The SPC for tadalafil gives specific information relating to the 2.5 and 5 mg doses in use with patients with renal and/or hepatic impairment. It states that 'due to increased tadalafil exposure, limited clinical experience and the lack of ability to influence clearance by dialysis, once-a-day dosing of tadalafil is not recommended in patients with severe renal impairment.[15] There is limited clinical data on the safety of single-dose administration of tadalafil in patients with severe hepatic insufficiency (Child-Pugh Class C). Once-a-day administration has not been evaluated in patients with hepatic insufficiency. If tadalafil is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.'[15] The SPC also makes mention of the cardiovascular risk, and regarding the lower once-a-day doses reports that 'in patients receiving concomitant antihypertensive medicinal products, tadalafil may induce a blood pressure decrease. When initiating daily treatment with tadalafil, appropriate clinical considerations should be given to a possible dose adjustment of the antihypertensive therapy.'[15]

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Tadalafil (Cialis®) once daily	**2.5 mg to 5 mg daily**	**Both £54.99 for 28**	**£716.84**
Tadalafil (Cialis®) when required	10 mg or 20 mg tablets at least 30 mins prior to sexual activity. Estimated once weekly.	Both strengths £26.99 for 4	If two tablets weekly: £701.74
Sildenafil (generic)	50 mg tablets approximately 1 hour prior to sexual activity. Estimated once weekly.	£1.03 for 4	If two tablets weekly: £26.78
Vardenafil (Levitra®)	10 mg tablet 25-60 minutes prior to sexual activity. Estimated once weekly	£14.08 for 4	If two tablets weekly: £366.08
Avanafil (Spedra®▼)	100 mg tablet approximately 15-30 minutes prior to sexual activity. Estimated once weekly	£14.08 for 4	If two tablets weekly: £366.08

Costs based on MIMS list prices January 2016. Table does not imply therapeutic equivalence of drugs or doses.

Associated additional costs or available discounts:

As this medication is already in use, additional associated costs are not a concern. There are no known available discounts.

Productivity, service delivery, implementation:

This is an alternative strength of a medication already available, and is already being prescribed; therefore it is unlikely to have an impact on service delivery. Prescribers would need to educate patients around the daily rather than on demand usage, and any AEs to be aware of, but this would form part of the normal review consultation.

Anticipated patient numbers and net budget impact:

National figures for the prescribing of PDE5 inhibitors for ED have not been accurately calculated by any of the national technology appraisal organisations – an estimate was produced when NICE issued its evidence review for avanafil in August 2014.[6] This used a Department of Health impact assessment on the removal of restrictions on the prescribing of generic sildenafil, produced in June 2014,[30] which estimated that 177,000 men are prescribed a PDE5 inhibitor within UK primary care at any one time. Using an estimated UK population of 64.6 million (Mid 2014 figure)[31] this equates to a figure of 284 patients per 100, 000 population.

According to the request received from the Contraception and Sexual Health service in Accrington, for the 12 month period 1/9/14 to 31/8/15 there were 135 referrals for men with ED. Of these, 16 received prescriptions for daily dose tadalafil, 4 of whom were discharged from the service requiring continuation of the medication. Of these 4, one fulfilled the criteria for SLS, two were early exits from the service and GPs were advised that continued prescribing was at their discretion as prescribers and the fourth was discharged onto a private prescription.

Prescribing data for Q2 14/15 to Q1 15/16 showed that there were 3930 items (Quantity x items = 113,941) for tadalafil 2.5 mg or 5 mg dispensed in primary care across Lancashire at a cost of £206,957.45. This indicates that the majority of prescribing is not initiated by the sexual health service. Generic versions of on demand and once daily tadalafil should become available from 2017 when the period of market exclusivity for Cialis® ends.

Innovation, need, equity:

The majority of the PDE5 inhibitors are be taken 'on demand' before anticipated sexual activity. Tadalafil is innovative as it is the only PDE5 inhibitor currently available which allows for daily administration and therefore more spontaneous rather than planned sexual activity.

Appendix A

Table: Summary of key tadalafil RCTs relevant to daily use in erectile dysfunction

Ref	Trial design	Patients / trial subjects	Trial intervention and comparison	Outcomes: Primary endpoint (mITT)	Outcomes: Key secondary / exploratory endpoints	Grading of evidence / risk of bias
Kim 2013[28]	Randomized, double-blind, parallel, placebo-controlled trial. 4 week PRN drug run in phase followed by a 4week non-drug washout phase prior to the 12 week treatment phase.	Sexually active men aged ≥18 years of age with a ≥3 month history of ED. Required to have taken maximum dose of sildenafil (100mg), vardenafil (20mg) or tadalafil (20mg) PRN for 1 month prior to study entry and have an IIEF-EF domain score of ≥17 and <26 at visit 1. Exclusion criteria were a IIEF-EF domain score ≥26 at visit 1 or 2 and prior ineffective treatment with any PDE5i in the opinion of the	Patients randomised to one of three treatment groups to take medication once daily. Tadalafil 2.5 mg titrated up to 5 mg: n=207 Tadalafil 5 mg: n=207 Placebo: n=209	Return to normal erectile function as measured by an IIEF-EF domain score ≥26. Statistically significant higher percentages of subjects with an IIEF-EF domain score in the normal range at end point compared with placebo group. (28.7% and 39.6% for 2.5 to 5mg and 5 mg tadalafil respectively compared to 12.1% for placebo, both p<0.001)	Evaluation of the efficacy measured by change from baseline to end point in: IIEF-EF domain score, (8.1 for 2.5 to 5 mg tadalafil, 8.0 for 5 mg, 1.9 for placebo. Both p<0.001) percentage of "yes" responses to SEP1, SEP2, SEP3,(2.5 to 5mg tadalafil 37.9%, 5 mg 40.1%, placebo 12.4% all p<0.001) SEP4 and SEP5 (all p<0.001 for both strengths against placebo); Confidence in the ability to get an erection as measured by IIEF question 15 (statistically significant for both tadalafil dose groups compared to placebo, all p<0.001); sexual satisfaction in men as	Patient-oriented outcome measure?: Yes Allocation concealment?: Yes Blinded if possible?: Yes Intention to treat analysis?: Yes Adequate power/size?: Yes Adequate follow-up (>80%)?: Yes Level 1 evidence based on high quality RCT with low risk of bias. Risk of bias: low based on Blinded concealed randomisation within severity bandings of a

		investigator, or no successful sexual attempts while using a PRN PDE5i in the 30 days prior to visit 1. Agreement to make at least 4 sexual intercourse attempts during the 5-week PRN run-in period and the 4-week nondrug run-in period, and no other ED treatments during participation in study. n=1021 screened for eligibility. n=623 subjects randomised to receive tadalafil or placebo. Baseline characteristics were well balanced across treatment groups.			measured by change IIEF Intercourse Satisfaction (IS) and Overall Satisfaction (OS) domains (both tadalafil treatment groups statistically significant improvements in the IIEF-IS and IIEF-OS domain scores compared with placebo, all p<0.001). Safety also assessed – nasal congestion was the only AE leading to discontinuation reported by more than one subject (2 subjects in tadalafil 2.5 to 5 mg group)	large adequately powered cohort of patients with around 90% subjects completing the study in each arm.
Porst 2006[19]	Randomised, double-blind, placebo-controlled, parallel-group, multi-centre 12	n=268. Patients ≥18 years of age, in monogamous relationship with a female partner, who reported ≥3 month history of	Daily administration of placebo (n=54), tadalafil 5 mg (n=109) or tadalafil 10 mg (n=105)	Three co-primary efficacy endpoints: Change from baseline in IIEF-EF domain score Placebo 15.0,	Percentage of 'yes' responses to the GAQ: 84.5% 5 mg, 84.6% 10 mg, 28.3% placebo p<0.001. Percentage of men who	Patient-oriented outcome measure?: Yes Allocation concealment?: Yes Blinded if possible?:

week study.	ED could be enrolled. Had to consent to not use other ED treatments during the study. Exclusions included: ED caused by other sexual or endocrine disorders such as premature ejaculation or hypogonadism; history of radical prostatectomy (except bilateral nerve-sparing prostatectomy) or other pelvic surgery with subsequent ED; clinically significant hepatobiliary or renal disease; haemoglobin A1c >13%; unstable cardiovascular disease; current nitrate use; congestive heart failure; recent significant central nervous system		tadalafil 5 mg 22.8, tadalafil 10 mg 22.8. p-value for both against placebo <0.001. Change from baseline in per-patient mean percentage of 'yes' response to SEP question 2 Placebo 51.7, tadalafil 5 mg 79.4, tadalafil 10 mg 81.2. p-value for both against placebo <0.001. Change from baseline in per-patient mean percentage of 'yes' response to SEP question 3 Placebo 36.7, tadalafil 5 mg 67.2, tadalafil 10 mg 72.8. p-value for both against placebo <0.001.	achieved an EF domain score of at least 26 ('no ED') at endpoint who had a baseline EF domain score below 26: 51.5% 5mg, 50.5% 10 mg, 8.3% placebo p<0.001. 5 and 10 mg taken once daily significantly improved EF as measured by all secondary efficacy variables	Yes Intention to treat analysis?: Yes Adequate power/size?: Yes Adequate follow-up (>80%)?: Yes Level 1 evidence based on randomised, blinded, adequate size, patient orientated outcome. Risk of bias: low based on adequate size, well randomised and blinded, allocation concealed.

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		injuries. Patients were ineligible if they had previously enrolled in any tadalafil study, or if they had prior ineffective treatment with sildenafil.				
Raifer 2007[20]	Randomised, double-blind, parallel-design study. A 4 week treatment free run in period prior to assessment of baseline characteristics then 24 weeks of treatment	n=287. Men aged 18 or over with at least 3 month history of ED (defined as consistent change in erection quality that adversely affects satisfaction with sexual intercourse) of psychogenic, organic or mixed origin, anticipating having the same adult female partner during the study and agreeing to at least 4 attempts at sexual intercourse during the 4-week treatment free run in period.	Patients randomised to placebo (n=94) tadalafil 2.5 mg (n=96) or tadalafil 5 mg (n=97) once daily.	Three co-primary endpoints were : Change from baseline to 24 weeks in mean IIEF-EF domain score. Larger changes observed for tadalafil 2.5 mg (6.1, $p<0.001$) and tadalafil 5 mg (7.0 $p<0.001$) compared to placebo group (1.2) Change from baseline to week 24 in mean per-patient percentage of 'yes' responses to SEP question 2. Tadalafil 2.5 mg 24.3%, tadalafil 5mg 26.2% and placebo 5.2% All $p<0.001$	Secondary efficacy endpoints included the 12-week change from baseline in IIEF-EF domain score, SEP2 and SEP3 as well as the 12 and 24 week change from baseline for IIEF intercourse satisfaction (IS) domain score (questions 6-8), IIEF overall satisfaction domain score (questions 13 and 14), IIEF question 3, IIEF question 4, Mean per-patient percentage of 'yes' response to SEP4 and SEP5, PAIRS sexual self-confidence and spontaneity domain scores, percentage of positive responses to GAQ1 ('has the treatment you have been taken during this study	Patient-oriented outcome measure?: Yes Allocation concealment?: unclear Blinded if possible?: Yes Intention to treat analysis?: Yes Adequate power/size?: yes Adequate follow-up (>80%)?: yes Level 2 evidence based on patient orientated outcome from randomised double blind trial, but uncertainty over allocation concealment.

| | | Exclusions include: if ED caused by premature ejaculation (PE) or untreated endocrine disease; failure to achieve erections following radical prostatectomy or other pelvic surgery; presence of penile implant or clinically significant penile deformity; clinically significant renal or hepatic insufficiency; several cardiac conditions as listed in the paper; blood pressure outside of predefined limits; recent history of stroke; spinal cord injury or other significant central nervous system injuries; HIV infection; current treatment with nitrates, cancer chemotherapy or antiandrogens; or recent history of drug, alcohol or | | compared to placebo. Change from baseline to week 24 in mean per-patient percentage of 'yes' responses to SEP question 3. Tadalafil 2.5 mg 31.2%, tadalafil 5 mg 35.1% and placebo 9.5%. All p<0.001 compared to placebo. | improved your erections') and GAQ2 ('if yes, has the treatment improved your ability to engage in sexual activity?') Also the proportion of patients with an IIEF-EF domain score <26 at baseline and ≥26 at endpoint indicating a return to normal erectile function. Tadalafil treatment significantly improved erectile function compared with placebo for all secondary study efficacy endpoints except the PAIRS spontaneity domain scores. | Risk of bias: moderate based on the uncertainty surrounding allocation concealment |

		substance abuse. Patients who had received previous ineffective treatment with PDE5i's in the opinion of the investigator based on patient medical history were also excluded.				
Hatzichristou 2008[21]	Randomised, double-blind, placebo-controlled, multicentre 12 week study.	n=298 adult men with at least 3 month history of diabetes and ED. In monogamous, heterosexual relationship and agree not to use any other ED treatment during run-in and treatment periods and for 96 hours after final study visit. Excluded if: HbA1c >13.0%, clinically significant renal or hepatic insufficiency, uncontrolled blood pressure, current	Once daily tadalafil 2.5 mg (n=100) or tadalafil 5 mg (n=98) or placebo (n=100)	Three primary efficacy measures. IIEF-EF domain score change from baseline Tadalafil 2.5mg 4.8, tadalafil 5mg 4.5, placebo 1.3 (changes ≥4 considered clinically meaningful) SEP2 tadalafil 2.5mg 20.5%, tadalafil 5mg 28.9%, placebo 5.3%. SEP3 tadalafil 2.5mg 25.9%, tadalafil 5mg 25.0%, placebo 8.2%.	Secondary endpoints included GAQ1, GAQ2, and percentage of men with 'no ED' after 12 weeks treatment. Tadalafil 2.5mg and 5mg taken once a day resulted in significant improvement compared with placebo in IIEF-IS and OS Domain scores, SEP4, Sep5 GAQ1 and GAQ2. All $p<0.001$ against placebo except IIEF-OS, 2.5mg vs placebo $p=0.002$, 5mg vs placebo 0.033. Those with IIEF-EF domain scores ≥26 at endpoint and thus 'no ED' was not statistically significant compared to placebo. 5mg vs placebo $p=0.104$, 2.5mg vs	Patient-oriented outcome measure?: yes Allocation concealment?: Blinded if possible?: yes Intention to treat analysis?: yes Adequate power/size?: yes Adequate follow-up (>80%)?: yes Level 1 evidence based on patient orientated, double blind randomised trial Risk of bias: low based on adequate size/power, good

		treatment with nitrates, recent history of serious unstable cardiovascular condition or stroke, any history of radical (except bilateral nerve-sparing) prostatectomy or other pelvic surgery with subsequent failure to achieve an erection.			placebo p=0.07.	follow up, blinded, allocation concealed.

Footnotes: IIEF-EF: International Index of Erectile Function – Erectile Function domain score. Stratified by result into mild (17-30), moderate (11-16) and severe (≤10). See appendix B for full details of the questions asked. PDE5i: Phosphodiesterase type 5 inhibitor, currently three licensed medications, sildenafil, tadalafil and vardenafil.

SEP: Sexual Encounter Profile, diary completed after each encounter. 5 questions detailed as follows: SEP1: "Were you able to achieve at least some erection (some enlargement of the penis)?" SEP2: "Were you able to insert your penis into your partner's vagina" SEP3: "Did your erection last long enough for you to have successful intercourse?" SEP4: "Were you satisfied with the hardness of your erection?" SEP5: "Were you satisfied overall with this sexual experience?"

IIEF-IS: International Index of Erectile Function – Intercourse Satisfaction domain score IIEF-OS: International Index of Erectile Function – Overall Satisfaction domain score AE: Adverse Event.

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Appendix B - The International Index of Erectile Function (IIEF-5) Questionnaire

Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res. 1999 Dec;11(6):319-26. © 1999 accessed at **http://www.hiv.va.gov/provider/manual-primary-care/urology-tool2.asp** 30/6/15

Over the past 6 months:					
1. How do you rate your confidence that you could get and keep an erection?	Very low 1	Low 2	Moderate 3	High 4	Very high 5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/always 5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time)4	Almost always/always 5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Extremely difficult 1	Very difficult 2	Difficult 3	Slightly difficult 4	Not difficult 5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/always 5

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: high quality randomised controlled trials (RCTs) with low risk of bias systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: clinical trials at moderate or high risk of bias systematic reviews or meta-analyses of such clinical trials or with inconsistent findings cohort studies case-control studies	
Level 3	Disease-oriented evidence, or evidence from: consensus guidelines expert opinion case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

Produced by:

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