This Primary Care Briefing has been produced to inform healthcare professionals in primary care of the new daily indication for tadalafil, which is used for erectile dysfunction, and to evaluate the supporting evidence.

What is tadalafil?
Tadalafil is a phosphodiesterase type 5 (PDE5) inhibitor.[1] When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 produces increased levels of cyclic guanosine monophosphate in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, producing an erection.

What is tadalafil licensed for?
Tadalafil (Cialis®) is licensed for the treatment of erectile dysfunction (ED) in men aged 18 years and over.[1]

Who can tadalafil be prescribed for?
Tadalafil can be prescribed on the NHS to treat ED in men with: diabetes, multiple sclerosis, Parkinson's disease, poliomyelitis, prostate cancer, severe pelvic injury, single gene neurological disease, spina bifida, spinal cord injury, renal failure treated with dialysis, or a man who has had: prostatectomy, radical pelvic surgery, renal failure treated by transplant. It can also be prescribed for men who were receiving a course of NHS drug treatment for ED on 14/09/98.[2;3] The prescription should be endorsed 'SLS'. Additionally the Department of Health recommends that men suffering severe distress on account of their ED should receive treatment on the NHS by specialist services (ref HSC 1999/177).

The Department of Health's guidance on the treatment of impotence (HSC 1999/148)[2] recommends to doctors that one treatment a week of a PDE5 inhibitor will be appropriate for most patients treated for erectile dysfunction. If the GP, in exercising his clinical judgement, considers that more than one treatment a week is appropriate, for example, the daily regimen of tadalafil for men having intercourse at least twice a week, he should prescribe that amount on the NHS. Tadalafil can also be supplied on a private prescription.

How is tadalafil given?
There are two dosing regimens for tadalafil:[1]

1. **On-demand regimen:** A 10mg dose is taken at least 30 minutes prior to anticipated sexual activity, increased to 20mg if necessary. The maximum dose frequency is once per day. These doses are not recommended for continuous daily use.
2. **Daily regimen:** Patient's who respond to on-demand treatment with any PDE5 inhibitor and who anticipate a frequent (at least twice a week) use of tadalafil, can take a lower daily dose. This should be based on patient choice and physician judgement. The recommended daily dose is 5mg, which can be reduced to 2.5mg according to tolerability. Continued use of the daily regimen should be reassessed periodically.

There is no direct head-to-head clinical trial evidence comparing once-daily with on-demand tadalafil. It is not possible to assess what the once-daily treatment offers in terms of clinical efficacy over on-demand treatment. One advantage of the daily regimen is that sexual activity can be separated from tablet taking.

Tadalafil has a longer half life than the other PDE5 inhibitors (17.5 hours compared with approximately 4 hours for sildenafil and vardenafil), which means it has a longer duration of action (up to 36 hours vs. 4-5 hours respectively).[4] Even if tadalafil 10-20mg were taken twice a week, there would be periods where the plasma concentration would be lower than if 5mg were taken daily and this may be subtherapeutic for some patients; this has not been studied in clinical trials. There is little difference, however, in the cost of 8x10mg/20mg tablets or 28x 2.5mg/5mg tablets.

How much does tadalafil cost?[5]
(a) On Demand regimen: 4 x 10mg or 20mg tablets: £26.99; 8 x 20mg tablets: £53.98
(b) Daily regimen: 28 x 2.5mg or 5mg tablets: £54.99

The cost-effective use of either "On demand" regimen or "Daily" regimen will depend upon the frequency of intercourse. The "Daily" regimen will most likely be more cost effective for the frequent users.

The Summary of Product Characteristics states that the 'on demand' dose is 10-20mg and the daily dose is 2.5-5mg. The SmPC does not state that 2x5mg cannot be used to obtain the 10mg 'on demand' dose.[1] Those patients that obtain tadalafil "On demand" by private prescription may notice that using 2x5mg from the daily 28 tablet pack is the most cost effective way to get a 10mg dose. If prescribed in this way for 4 weeks, treatment costs for e.g. 8 x 10mg = £53.98 or 16 x 5mg = £31.42. This is equivalent to a £290 saving per patient p.a. (42% price reduction).

Cautions and contraindications

There are a number of cautions, contra-indications, drug interactions and assessments that need to be considered before prescribing tadalafil. These can be found in detail in the Summary of Product Characteristics.

What did the main trials of daily tadalafil show?

Three main randomised, placebo-controlled studies have evaluated the efficacy of once-daily tadalafil.[6-8] Patients were excluded if they had not responded to PDE5 inhibitors in the past. Once-daily tadalafil was not compared with on-demand tadalafil. Men with diabetes were enrolled in each of the three studies, however, one study enrolled men exclusively with type 1 and 2 diabetes, with the majority having type 2.[7] In all three studies tadalafil significantly and clinically improved erectile function (EF), regardless of baseline severity. Significantly more men using tadalafil than those using placebo had successful intercourse. Overall, daily tadalafil significantly improved various aspects of patient satisfaction, including overall satisfaction with treatment and with sexual experience. Although less than half of men with diabetes were able to have successful intercourse, the percentages had improved significantly from baseline. Tadalafil 5mg was well tolerated and effective in 1- and 2-year open-label extension studies, with no serious adverse events considered related to tadalafil use.[9] Further trial details are in the Appendix.

The numbers needed to treat to enable an extra patient to achieve successful intercourse are in table 1: for 5mg tadalafil the NNT is ~5 patients. These are based on the numbers of patients saying 'yes' to the Sexual Encounter Profile question 3: did your erection last long enough for you to have successful intercourse? The numbers are higher in the study by Hatzichristou et al; randomisation did not take into account the type of diabetes the patients had and the results may have been different if equal numbers of type 1 and type 2 diabetic patients had been enrolled.[7]

Table 1: Primary efficacy results from the once-daily tadalafil studies.

		SEP 3 'Yes' at endpoint	Number needed to treat
Porst et al[6] 12 week study	Placebo (n=54)	36.7%	-
	5mg (n=109)	67.2%*	3.3
	10mg (n=105)‡	72.8%*	2.8
Hatzichristou et al[7] 12 week study, type 1 and 2 diabetes	Placebo (n=100)	28.2%	-
	Tadalafil 2.5mg (n=100)	46.0%†	5.6
	Tadalafil 5mg (n=98)	41.1%†	7.7
Rajfer et al[8] 24 week study	Placebo (n=94)	31.3%	-
	Tadalafil 2.5mg (n=96)	50.0%*	5.3
	Tadalafil 5mg (n=97)	56.9%*	4
* p<0.001 † p≤0.005 ‡10mg not licensed for daily use			

References
(1) Summary of Product Characteristics. Cialis 2.5mg, 5mg, 10mg & 20mg film-coated tablets. Eli Lilly and Company. Date of revision of the text: 03 September 2008. Accessed via http://emc.medicines.org.uk on 12/03/09.
(2) Health Service Circular HSC 1999/148. Treatment for impotence. 30th June 2000. Accessed via http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Healthservicecirculars/DH_4004766 on 12/03/09.
(3) British National Formulary, 57th edition. March 2009. Ed. Martin J. British Medical Association and Royal Pharmaceutical Society of Great Britain. Accessed via www.bnf.org on 24/04/09.
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(6) Porst H, Giuliano F, Glina S et al. Evaluation of the efficacy and safety of once-a-day dosing of tadalafil 5mg and 10mg in the treatment of erectile dysfunction: results of a multicenter, randomized, double-blind, placebo-controlled trial. Eur Urol 2006; 50:351-359.
(7) Hatzichristou D, Gambla M, Rubio-Aurioles E et al. Efficacy of tadalafil once daily in men with diabetes mellitus and erectile dysfunction. Diabet Med 2008; 25:138-146.
(8) Rajfer J, Aliotta PJ, Steidle CP et al. Tadalafil dosed once a day in men with erectile dysfunction: a randomized, double-blind, placebo-controlled study in the US. Int J Impot Res 2007; 19(1):95-103.
(9) Porst H, Rajfer J, Casabe.A. et al. Long-term safety and efficacy of tadalafil 5mg dosed once daily in men with erectile dysfunction. J Sex Med 2008; 5:2160-2169.

$$\text{NNT:} \quad \cfrac{1}{\cfrac{\text{'Intervention' 'Yes' outcome}}{\text{Total 'Intervention'}} - \cfrac{\text{'No intervention' 'Yes' outcome}}{\text{Total 'No intervention'}}}$$

[Usually NNTs show how many patients need to be treated with the intervention to prevent the outcome; in this case the outcome is required.]

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What did the main trials of daily tadalafil show?

Three main randomised, placebo-controlled studies (2x12 week, 1x24 week) have evaluated the efficacy of once-daily tadalafil.[6-8] Over 80% patients enrolled were Caucasian and the mean age was 56-57 years. Exclusion criteria included current nitrate use, cardiac disease and non-response to PDE5 inhibitors. In the first 12-week study 268 men were randomised to daily placebo, tadalafil 5mg or tadalafil 10mg.[6] In the second, 298 men with diabetes (88.9% with type 2), were randomised to daily placebo, tadalafil 2.5mg or tadalafil 5mg.[7] In the 24-week trial 287 men were also randomised to daily tadalafil 2.5mg, 5mg or placebo.[8]

The 3 primary efficacy measures were the International Index of Erectile Function – Erectile Function domain (IIEF-EF), to assess the severity of ED, and the percentage of 'yes' responses to the Sexual Encounter Profile (SEP) questions 2 (were you able to insert your penis into your partner's vagina) and 3 (did your erection last long enough for you to have successful intercourse). There were a number of secondary endpoints, which included the percentage of men with 'no ED' (IIEF-EF domain score 26-30).

In all studies tadalafil significantly and clinically improved erectile function (EF), as measured by all three primary efficacy measures. Analyses of ED by severity (mild, moderate and severe) showed improvements in EF regardless of baseline severity. Significantly more patients taking tadalafil than those taking placebo answered 'yes' to SEP questions 2 and 3, (see table 1). Although less than half of men with diabetes were able to have successful intercourse, the percentages had improved significantly from baseline (see table 1).[7] Overall, daily tadalafil significantly improved various aspects of patient satisfaction, including overall satisfaction with treatment and with sexual experience. None of the studies compared the daily regimen with the on-demand regimen. Some increase in efficacy might be expected with the daily dosing compared with the on-demand dosing, as the plasma concentrations of tadalafil are 1.6 fold greater.[8] The efficacy of 5mg daily appears to be comparable to the 10mg on-demand dose, though there are no direct comparisons. In the longer term trial[8], the efficacy results seen at week 24 were similar to those at week 12; there was no evidence of tolerance or treatment resistance to tadalafil.

In the trial by Porst et al[6], men with an IIEF-EF score ≥26 were included in the primary analysis, which is consistent with clinical practice; excluding these patients did not affect the statistical interpretation of the data. In the trial by Hatzichristou et al[7], the variations in diabetes characteristics between the tadalafil dose groups did not change the size of the treatment effect, though it was suggested that randomisation should take variations into account.[7] The results may have been different if equal numbers of type 1 and type 2 diabetic patients had been enrolled.

Table 1: Primary efficacy results from the once-daily tadalafil studies.

		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[6]	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[7]	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[8]	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.

Open-label extensions of the 12- and 24-week studies by Porst and Rajfer evaluated the long-term safety and efficacy of daily tadalafil.[9] In the 1-year extension, 183 completers of the 268 originally enrolled and in the 2-year study 238 completers of the 287 originally enrolled, continued with a 5mg tadalafil dose. Cumulative tadalafil exposures were 225.1 and 355.5 patient years for the 1- and 2- year extensions respectively. No unexpected safety issues were seen and neither the two deaths that occurred nor any of the serious adverse events (SAEs) were considered related to tadalafil use. SAEs occurred in 36 patients (7.6%), with 9 experiencing a total of 10 cardiovascular events

(cerebrovascular accident, coronary artery disease, myocardial infarction, atrial fibrillation, worsening hypertension and syncope). Eight of these events occurred in patients with known cardiac disease.

The incidence rates of MI were 0.44/100 patient-years and 0.28/100 patient-years for the 1- and 2-year extension studies, which are lower than previously reported for tadalafil and sildenafil, as well as lower than those reported for men in the general population (0.61/100 patient-years for men aged 45-54 years old and 2.25/100 patient-years for men aged 75-84 years old). Treatment-emergent AEs occurred in 53.4% and 71.8% of patients in the 1- and 2- year extensions, and included dyspepsia, headache and back pain, all of which are associated with PDE5 inhibitor use.

Tadalafil efficacy was maintained for up to 2 years. The mean IIEF-EF domain score improved from 13.7 at baseline to 24.1 at the end of the 1-year study, and from 14.0 to 24.8 at the end of the 2-year study, indicating an improvement from moderate to mild EF. 'Normal' EF (IIEF-EF score ≥26) was achieved by 57.8% of men with evaluable data. Four weeks after discontinuing tadalafil, only a quarter of men had maintained 'normal' erectile function. Response rates to the Global Assessment Question 1 (has the treatment improved your erections) and question 2 (if yes to GAQ 1, has the treatment improved your ability to engage in sexual activity) were 95.7% and 92.1% (2-year extension only). Thirty five of the 47/472 men who discontinued because of lack of efficacy had severe ED at baseline.

Overall, the long-term results show that tadalafil is safe and effective and a viable alternative to the on-demand regimen for those who prefer spontaneous rather than scheduled sexual activity.

References:

(1) Summary of Product Characteristics. Cialis 2.5mg, 5mg, 10mg & 20mg film-coated tablets. Eli Lilly and Company. Date of revision of the text: 03 September 2008. Accessed via http://emc.medicines.org.uk on 12/03/09.

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