

DRUG UPDATE

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PDE5 INHIBITORS FOR ERECTILE DYSFUNCTION

Sildenafil, tadalafil and vardenafil are phosphodiesterase type 5 inhibitors licensed for the treatment of erectile dysfunction in the presence of sexual stimulation. There is no evidence of any clinically important differences in efficacy between these agents. Sildenafil has a good safety profile based on substantial patient years of experience. Tadalafil has a longer half life than sildenafil. Patient preference is likely to influence treatment selection.

What is it?

Sildenafil (Viagra[®], Pfizer) is an oral phosphodiesterase type 5 (PDE5) inhibitor that has been available for the treatment of male erectile dysfunction since 1998. Two more PDE5 inhibitors; tadalafil (Cialis[®], Lilly) and vardenafil (Levitra[®], Bayer and GlaxoSmithKline) were launched in February 2003 and March 2003 respectively. They should all be taken shortly before sexual activity (one hour, 30 minutes and 25 - 60 minutes respectively). There is evidence from several clinical trials of an effect of tadalafil at 24 and 36 hours post dose.^{1,2}

How effective are they?

Sildenafil – Since its launch sildenafil has been prescribed to more than 20 million patients worldwide.³ Response rates to the global efficacy question for men with predominantly psychogenic or organic disease are reported to be 84% and 68% respectively.⁴ The efficacy of sildenafil has been assessed in open label extension studies (1 to 3 years), where more than 95% of patients reported that they were satisfied with the effect of treatment on their erections.³

Tadalafil – Six randomised, double-blind studies have compared tadalafil with placebo.² In a pooled analysis of five of the studies, (n=1,112) men with mild to severe erectile dysfunction of various etiologies were randomised to tadalafil 10 mg and 20 mg or placebo for 12 weeks.¹ The licensed dose is 10 mg (range 10-20 mg) Efficacy was primarily assessed using the International Index of Erectile Function (IIEF*) Tadalafil compared to placebo increased the score from baseline (6.5 vs. 7.9 vs. 0.6 p<0.001). The percentage of men achieving erections increased from baseline (24% vs. 27% vs. 2% p<0.001) and those maintaining erections increased from baseline (34% vs. 39% vs. 6%, p<0.001). In the sixth study (n=191), tadalafil significantly enhanced erectile function in men with diabetes and ED.⁵

Vardenafil – Four randomised, double blind studies have compared placebo with vardenafil.⁶ In a large randomised, double blind, placebo controlled study (n=805) in a broad population of men with ED of various etiologies and severity, vardenafil 5 mg, 10 mg and 20 mg (the licensed dose is 10 mg (range 5-20 mg)) was compared to placebo for 26 weeks. The IIEF score improved from baseline (5.3 vs. 7.8 vs. 9.0 vs. 1.2, p £0.001).⁷ The percentage of men achieving erections increased from baseline (23% vs. 30% vs. 40% vs. 6%, p< 0.0001) and those maintaining erections increased from baseline (38% vs. 50% vs. 52% vs. 18%, p<0.0001)

Comparative efficacy

There are no published clinical trials comparing the efficacy of sildenafil, tadalafil and vardenafil. Comparison of efficacy is difficult because patient populations and trial designs are different.

How safe are they?

The most frequently reported adverse events after sildenafil use include: headache, flushing and dyspepsia.⁸ Recent studies have shown that sildenafil does not worsen the cardiac profile of patients with ischaemic heart disease undergoing stress exercises.⁸ Transient visual disturbances of colour vision have been reported mainly at the 100 mg dose and occur when plasma concentrations are at their peak.⁸

The side effect profile for vardenafil appears to be similar to that of sildenafil.⁸

Patients taking tadalafil reported headache, dyspepsia and back pain as the most frequent adverse events.⁸ Daily use of this agent is not recommended because the long-term safety after prolonged daily dosing has not been established.⁹

In clinical trials of vardenafil vs. placebo and tadalafil vs. placebo there was a low rate of discontinuation due to adverse events (5.2% vs. 2.2% and 2.1% vs. 1.3% respectively).^{1,7} All three drugs are contraindicated in patients taking nitrates, as coadministration can result in a significant drop in blood pressure.^{9,10,11}

* IIEF is a self-administered questionnaire that assesses 5 domains of male sexual function, on a 5 to 6-point scale, in which higher scores signify better sexual function.

What other options are there?

Alprostadil is available for intracavernosal injection and transurethral administration. Recently sublingual apomorphine has been licensed for the treatment of erectile dysfunction.

When should they be used?

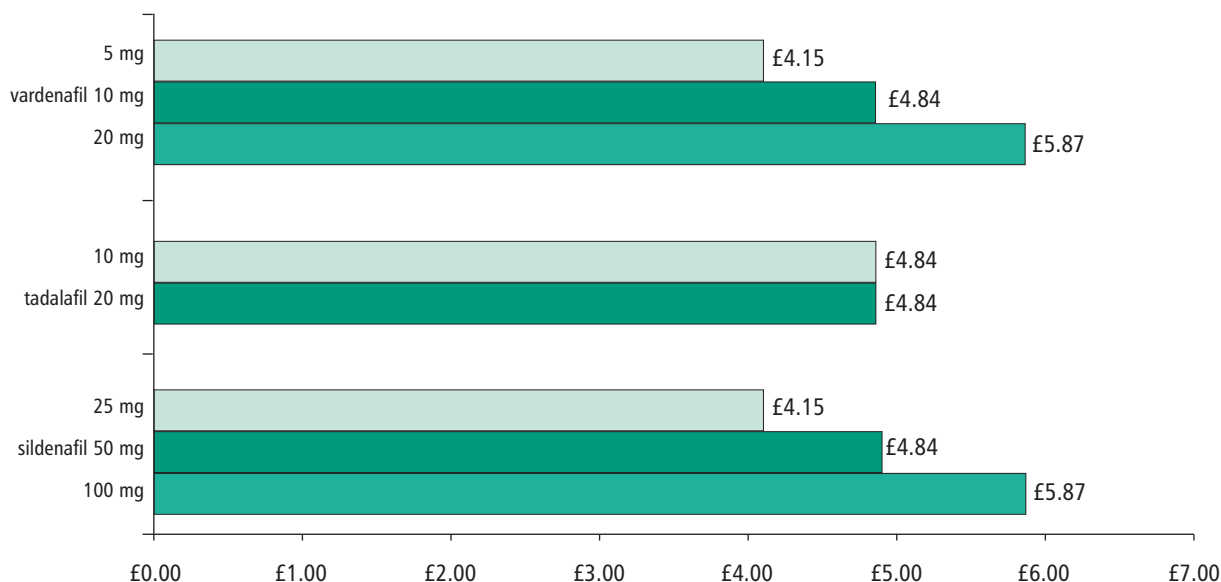
There is no evidence of any clinically important differences in efficacy between these agents. Sildenafil has more long term safety data as it has been available since 1998. Tadalafil appears to be longer acting than the other two agents. Patients should choose a suitable treatment based on a discussion with their medical

advisor about the advantages and disadvantages of each treatment.¹²

GPs are able to write FP10 prescriptions for impotence treatments for men undergoing therapy for prostate cancer or for those who have had a prostatectomy or those with spinal cord injury, renal failure, diabetes, multiple sclerosis, single gene neurological disease, spina bifida, polio, Parkinson's disease and severe pelvic injury. Men who were receiving treatment for impotence before 14th September 1998 but not included in the above categories are also eligible. The Department of Health (England) has also recommended that treatment should be available from specialist services when the condition is causing severe distress.¹³

How much does it cost?

Cost for one dose (prices from MIMS August 2003)



NB agents shown are for general comparison only and do not imply therapeutic equivalence

REFERENCES

- 1 Brock GB et al. Efficacy and safety of tadalafil for the treatment of erectile dysfunction; results of an integrated analysis. *J Urol* 2002;168:1332-6.(MA)
- 2 The European Agency for the Evaluation of Medicinal Products. Committee for Proprietary Medicinal Products European Public Assessment Report (EPAR) Tadalafil. <http://www.eudra.org/emea.html>. Cited May 2003. (R)
- 3 Carson CC et al. The efficacy of sildenafil citrate (Viagra®) in clinical populations: an update. *Urology* 2002;60 (Suppl 2B):12-27.(R)
- 4 Osterloh IH and Riley A, Clinical update on sildenafil citrate. *Br J Clin Pharmacol* 2002;53:219-23.(R)
- 5 Saenz de Tejada I et al. Effects of tadalafil on erectile dysfunction in men with diabetes. *Diabetes Care* 2002;25:2159-64.(RCT)
- 6 The European Agency for the Evaluation of Medicinal Products. Committee for Proprietary Medicinal Products European Public Assessment Report (EPAR) Vardenafil. <http://www.eudra.org/emea.html>. Cited May 2003.(R)
- 7 Hellstrom WJG et al. Vardenafil for the treatment of men with erectile dysfunction: efficacy and safety in a randomised, double blind, placebo controlled trial. *J Androl* 2002;23:763-71.(MA).
- 8 Montorsi F et al. Pharmacological management of erectile dysfunction. *BJU International* 2003;91:446-54.(R)
- 9 Viagra. Summary of Product Characteristics. Pfizer. September 1998.
- 10 Cialis. Summary of Product Characteristics. Lilly. November 2002.
- 11 Levitra. Summary of Product Characteristics. Bayer. March 2003.
- 12 Ralph D and McNicholas T. UK management guidelines for erectile dysfunction. *BMJ* 2000;321:499-503.
- 13 British National Formulary 45. March 2003

KEY RCT - randomised controlled trial, CT-controlled trial, O-open study, MA-meta analysis, R-review, U-unpublished, Abs- abstract, E-editorial