QIPP Detail Aid Support Document

Providing support for quality in prescribing

Sildenafil- a generic opportunity

KEY MESSAGES

- **Sildenafil came off patent in June 2013 and the cost of generic tablets has fallen dramatically. Ensure that all prescriptions for sildenafil are written generically.**
- **Consider switching appropriate patients taking tadalafil or vardenafil to generic sildenafil. Daily tadalafil is expensive and is not recommended.**
- **Prescribing of treatments for erectile dysfunction on the NHS is still based on Dept Health guidance (1999), which restricts who can receive treatment and recommends one treatment per week for the majority of patients.**
- **Generic sildenafil should be the first line option for all new patients if prescribing is considered appropriate after full investigation of underlying causes.**

WHAT IS THE PROBLEM?

- *Within the Barnsley area, approximately £435k was spent on oral phosphodiesterase type-5 (PDE5) inhibitors for erectile dysfunction in 2012-13. Approximately 53% of this spend was for sildenafil and 43% for tadalafil with just 4% on vardenafil.*

BNF Name	Total Items	Total Act Cost
Sildenafil	8,767	£230,329 (£3,143 of which was prescribed as Viagra)
Tadalafil	5,195	£185,280
Vardenafil	832	£19,796
Total	***14,794***	***£435,396***

- *Sildenafil came off patent in June 2013 and the cost of generic tablets has fallen dramatically.*

  The cost of sildenafil in the Drug Tariff, October 2013, is now 92% lower than the branded Viagra prices.

- *This will lead to a saving of £191k in the South Yorkshire area if prescribing rates stay the same, provided all scripts are written generically. A further approximately £195k could be saved if all PDE5 inhibitor prescribing was switched to generic sildenafil.*

  We have assumed a switch at the following dose conversions. Note that, as there are no comparative trials between agents, these are pragmatic dose equivalent choices, based on licensed dosage ranges, not necessarily therapeutically equivalent doses:

Drug	Switch to:
Tadalafil 10mg	Sildenafil 50mg
Tadalafil 20mg	Sildenafil 100mg
Tadalafil 2.5mg daily	Sildenafil 100mg 8 per month (NB high dose chosen to compensate for loss of daily dosage.)
Tadalafil 5mg daily	Sildenafil 100mg 8 per month (NB high dose chosen to compensate for loss of daily dosage.)
Vardenafil 5mg	Sildenafil 25mg
Vardenafil 10mg	Sildenafil 50mg
Vardenafil 20mg	Sildenafil 100mg

Endorsed by the Area Prescribing Committee November 2013

WHAT IS THE EVIDENCE?

- *There are no head-to-head studies between the three oral PDE5 inhibitors. A systematic review in 2009 found no differences between the drugs in efficacy or adverse effects.*

  The systematic review and meta-analysis included randomised controlled trials of pharmacologic treatments (PDE5 inhibitors and testosterone) compared to each other or placebo in men aged 18 years or over with erectile dysfunction[2]. Most studies had a follow-up of 12 weeks or less. Mean age was 18 to 69 years, where reported. Most trials excluded men with penile/testicular deformity, cardiovascular comorbidity, prostate cancer, HIV/AIDS, hepatic/renal disease, spinal cord injuries and psychiatric disorders. Several vardenafil and tadalafil trials excluded men who were non-responsive to sildenafil treatment.
  One hundred and thirty RCTs evaluated PDE5 inhibitors (n=approximately 35,000). All PDE5 inhibitors consistently improved erectile functioning compared to placebo: 73% to 88% of men who received PDE5 inhibitors experienced improved erectile function compared with 26% to 32% of men who received placebo. Pooled relative risks for a general population of men with erectile dysfunction were: sildenafil 2.50 (95% CI 2.27 to 2.76; 19 RCTs, n=4,841); vardenafil 2.73 (95% CI 2.46 to 3.04; 11 RCTs, n=4,332); tadalafil 2.62 (95% CI 2.15 to 3.18; 13 RCTs, n=3,071). Further results were reported, including: improvements from baseline in successful intercourse attempts and results for subgroups (men with co-morbidities, different dosing regimens, different severity of baseline erectile dysfunction). There was no statistically significant difference in the incidence of adverse events among men treated with sildenafil, vardenafil, and tadalafil. The authors concluded that all oral PDE5 inhibitors had similar efficacy and safety profiles.

- *There are some differences between agents in how they are taken and licensed indications. They are taken either 60 minutes (sildenafil), 25-60 minutes (vardenafil) or at least 30 minutes (tadalafil) before anticipated sexual activity. Tadalafil has a longer serum half life that the other agents and thus has a longer duration of effectiveness (up to 36 hours) compared with 4-5 hours for sildenafil. This may be of benefit for some, but not all patients.*

	Sildenafil[3-4]	**Vardenafil[3,5]**	**Tadalafil[3,6]**
Maximum frequency	Once daily	Once daily	Once daily
Time taken before sexual activity	1 hour	25-60 minutes	At least 30 minutes
Tmax	30-120 mins (median 60mins) (fasted state)	30-120 mins (median 60 mins) (fasted state)	0.5-6 hours (median 2 hours)
Time to erection	25 mins (range 12-37 mins)	25 mins (range from 15mins)	30-45 mins (range from 16mins)
Time still able to produce erection post dose	4-5 hours	4-5 hours	Up to 36 hours

- *Tadalafil is licensed for daily dosing, however this is very expensive and in many areas is considered non-formulary. Dept of Health guidance recommends one treatment per week at NHS expense for the majority of patients.*

  In the original guidance on the 'treatment of impotence' (HSC 1999/148)[7] the Dept Health (DH) advised doctors that one treatment a week will be appropriate for most patients treated for erectile dysfunction. If the GP in exercising clinical judgement considers that more than one treatment a week is appropriate they should prescribe that amount on the NHS. This was based on evidence which showed that the average frequency of sexual intercourse in the 40-60 age range is once a week. The DH also cautioned that PDE5 inhibitors may have a "street value" for men who consider that these treatments will enhance their sexual performance and that excessive prescribing could therefore lead to unlicensed, unauthorised and possibly dangerous use of these treatments.

- *The prescribing of treatments for erectile dysfunction (ED), in terms of who is eligible, is restricted under the NHS. Prescribers should ensure that any underlying conditions, for example drug-induced ED or diabetes are identified in patients who present for the first time with ED. In some cases, treating the underlying condition can lead to resolution of ED. The British Society for Sexual Medicine have produced guidance on investigations that might be undertaken in men newly presenting with ED and provides a list of drugs known to cause ED.*

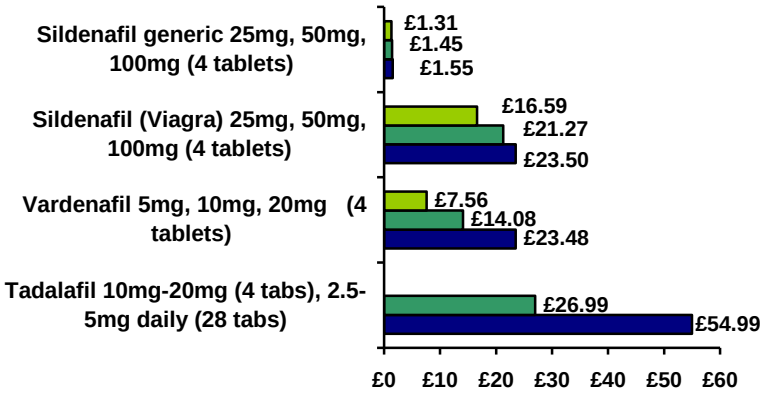
  The criteria for prescribing treatment for ED on the NHS are laid down in HSC 1999/115[8] and are also available in the BNF. Broadly they include the following:
  - men who have had radical pelvic surgery; men who have had their prostate removed and / or have been treated for prostate cancer (surgery and other treatment); treated for renal failure (transplant and dialysis); spinal cord and severe pelvic injury; diabetes; multiple sclerosis; single gene neurological disease, poliomyelitis, spina bifida and Parkinson's disease.
  - men not included in the above categories but who were receiving treatment for impotence on 14 September 1998.
  - men diagnosed to be suffering from severe distress on account of their impotence should be referred to specialist services who will prescribe treatment if it is considered appropriate.

An enlarged prostate alone is not included in the clinical conditions list but audit data suggests such patients have been receiving NHS treatment in certain areas of the UK.

The BSSM guidelines[9] note that drugs may affect sexual response in a number of ways:

- drugs that cause sedation may affect sexual motivation and, indirectly, cause ED
- drugs that affect CV function, such as antihypertensive agents, may act centrally and may also affect penile haemodynamics
- some drugs affect endocrine parameters; anti-androgens and oestrogens may affect both sexual desire and erection
- drugs that cause hyperprolactinaemia, such as phenothiazines, may also affect sexual desire and erection.

WHAT ARE THE COSTS?



Costs from MIMS/ Drug Tariff October 2013
Doses given are a guide only and are based on licensed doses.

Prescribing Information

On the 1st October 2013, The Department of Health issued amended regulations for the prescribing of drugs normally indicated for the treatment of erectile dysfunction, and the Drug Tariff has been amended.

The new regulations remove reference to brand names and now cover all presentations of the active ingredient, regardless of whether a branded or generic prescription is being dispensed. This also covers all formulations of a drug

Prescribers must endorse prescriptions with SLS (Selected List Scheme) for any items appearing in the SLS list; where this isn't present pharmacists are instructed to return prescriptions to the prescriber for their correct endorsement in order for it to be dispensed and reimbursed.

The SLS list' (Schedule 2 of The National Health Service (General Medical Services Contracts) (Prescription of Drugs etc) is as follows:

- Alprostadil
- Apomorphine Hydrochloride
- Moxisylyte Hydrochloride
- Sildenafil
- Tadalafil
- Thymoxamine Hydrochloride
- Vardenafil

For patients who do not meet the SLS criteria and are therefore unable to receive on NHS prescription, sildenafil could be considered as a cost-effective alternative for patients who have to pay for vardenafil or tadalafil on private prescription.

References:

1. MHRA Public Assessment Reports for medicines (available from www.mhra.gov.uk/Publications/PublicAssessmentReports, Accessed 28th February 2013)
2. Tsertsvadze A, Fink HA, Yazdi F, MacDonald R, Bella AJ, Ansari MT, Garritty C, Soares-Weiser K, Daniel R, Sampson M, Fox S, Moher D, Wilt T. Oral phosphodiesterase-5 inhibitors and hormonal treatments for erectile dysfunction: a systematic review and meta-analysis. Annals of Internal Medicine 2009; 151(9): 650-661

3. DRUGDEX® System: Klasco RK (Ed). DRUGDEX® System. Thomson Micromedex (Greenwood Village, Colorado, updated periodically). Available from www.thomsonhc.com [accessed on-line 28th February 2013]

4. 16 January 2013 Viagra 25mg, 50mg, 100mg tablets—Summary of Product Characteristics [online], *Pfizer Ltd*. Available from www.medicines.org.uk [accessed on-line 28th February 2013].

5. 21st February 2012 Levitra 5mg, 10mg, 20mg film-coated tablets Summary of Product Characteristics [online], Bayer plc. Available from www.medicines.org.uk [accessed on-line 28th February 2013].

6. 17 January 2013 Cialis 2.5mg, 5mg, 10mg & 20mg film-coated tablets Summary of Product Characteristics [online], Eli Lilly and Company Limited Available from www.medicines.org.uk [accessed on-line 28th February 2013].

7. Anon Dept Health Treatment of impotence' HSC 1999/148 (Available from http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4012086.pdf, Accessed 28th February 2013)

8. Anon Dept Health Treatment of impotence' HSC 1999/115 (Available from http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4012070.pdf, Accessed 28th February 2013)

9. British Society for Sexual Medicine Guidelines on the management of erectile dysfunction 2009 (available from http://www.bssm.org.uk/downloads/BSSM_ED_Management_Guidelines_2009.pdf, Accessed 28th February 2013)

10. Change in prescribing guidance for the treatment of erectile dysfunction October 2013 www.psnc.org.uk/our-news/change-in-prescribing-guidance-for-drugs-for-the-treatment-of-erectile-dysfunction/