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TRENT MEDICINES INFORMATION SERVICE

QIPP Detail Aid Support Document

Providing support for quality in prescribing

Sildenafil- a generic opportunity

KEY MESSAGES

- **Sildenafil will come off patent in June 2013. 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 East Midlands, £6 million was spent on oral phosphodiesterase Type-5 (PDE5) inhibitors in 2012. Approximately half of this spend was for sildenafil and half for tadalafil with a small amount on vardenafil.*

BNF Name	Total Items	Total Act Cost	
Sildenafil	108,221	£2,948,039	(£101,576 of which is currently prescribed as Viagra)
Tadalafil	74,564	£2,576,227	
Vardenafil	17,855	£396,766	
	200,640	***£5,921,032***	

- *Sildenafil will come off patent in June 2013; generic tablets are expected soon afterwards and the cost of generic sildenafil is predicted to fall.*

  To date, six generic sildenafil products have been approved by the EMA or MHRA[1]. Although we do not have any insight into launch plans of these products, it would be expected that at least some of these will be launched on or soon after the expiry of the patent. The Drug Tariff price may be expected to fall a few months later.

- *If the pattern follows other generic launches the price could drop by at least 50%. This would lead to a potential saving of £1.5million in the East Midlands if all scripts are written generically. A further £1.6million could be saved if all PDE5 prescribing was switched to generic sildenafil if the price falls as expected..*

  A 50% reduction in price was chosen as a simple comparator. The price of generic sildenafil will not be known until after the launch of generic products. However, previous generic launches have shown price reductions of at least this level; the price of generic atorvastatin fell by 74% compared to the brand product.
  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 (NB assuming a 50% decrease in sildenafil prices with generics, vardenafil is still cheaper than sildenafil 25mg)
Vardenafil 10mg	Sildenafil 50mg
Vardenafil 20mg	Sildenafil 100mg

Date of Preparation: March 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 of the East Midlands 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.*

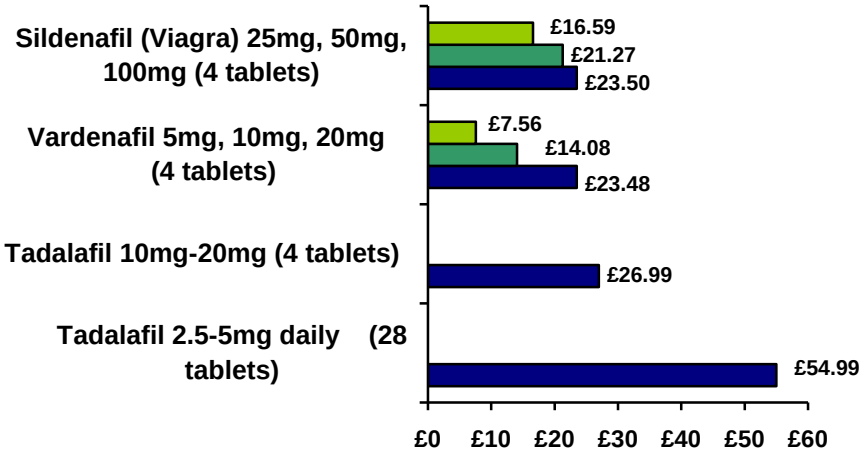
  The criteria for prescribing treatment for ED on the NHS are laid down in HSC 1999/115[8] and are also available in the BNF. Broadly they include the following:
  - men who have had radical pelvic surgery; men who have had their prostate removed and / or have been treated for prostate cancer (surgery 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 March 2013
Doses given are a guide only and are based on licensed doses.

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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)