NHS
Wakefield
Clinical Commissioning Group

Commissioning Statement

Treatment	**Phosphodiesterase type-5 inhibitors** Sildenafil; Tadalafil; Vardenafil
For the treatment of	**Penile rehabilitation post radical prostatectomy**

Commissioning position	**Wakefield CCG commissions the use of generic sildenafil for penile rehabilitation post radical prostatectomy, only if the following conditions apply:**
	
	• The patient has undergone radical prostatectomy
	• Treatment must be initiated by a specialist in urology and continued only if the patient responds favourably:
	  ○ The patient is reviewed regularly and treatment stopped if patient does not maintain adequate response
	  ○ Treatment is continued for up to 12 months
	
	Wakefield CCG does not routinely commission the use of other PDE5 inhibitors for penile rehabilitation.
	
	There is some evidence that PDE5 inhibitors may improve penile rehabilitation following radical prostatectomy. Other PDE5 agents are restricted for use to an on required basis for erectile dysfunction.
	
	The criteria for NHS prescribing of PDE5 inhibitors for the management of erectile dysfunction by GPs is set out in Part XVIIIB of the Drug Tariff

Date effective from	October 2014
Policy to be reviewed by	October 2017

Background information	Phosphodiasterase type-5 (PDE5) inhibitors are licensed for the treatment of erectile dysfunction (ED). ED is a common complication following a prostatectomy due to cavernosal nerve damage, which can occur even after nerve-sparing surgery (1). Supportive therapy to rehabilitate erectile function should be started as early as possible (1;2;3). Clinical trial evidence supports the use of PDE5 inhibitors for up to 12 months after prostatectomy. **National Guidance:** The recommended dosing of sildenafil, tadalafil and vardenafil is one dose prior to sexual activity; the maximum recommended dosing frequency is once a day (2). PDE5 inhibitors can be prescribed on the NHS following prostatectomy for the treatment of impotence (4), normally allowing for one dose per week. However, the regulations allow the prescribing doctor to prescribe more than one dose a week if judged clinically appropriate. The daily use of a PDE5 inhibitor is within the licensing of all these drugs. The licence for tadalafil states that it is intended for use prior to anticipated sexual activity and it is not recommended for continuous daily use and suggests a dose of 2.5mg or 5mg if it is to be used in this way, based on tolerability and clinical judgment. The appropriateness of continued use of the daily regimen should be reassessed periodically (2). NICE CG175 (5) states that men with prostate cancer who experience loss of erectile function (following prostatectomy) should be offered PDE5 inhibitors to improve their chance of spontaneous erections. PDE5 inhibitors should also be offered to men having long-term androgen deprivation therapy who experience loss of erectile function. The guideline goes on to state that if PDE5 inhibitors fail to restore erectile function or are contraindicated, men should be offered either vacuum devices, intraurethral inserts or injections or penile prostheses as an alternative. The Scottish Medicines Consortium (SMC) have not considered PDE5 inhibitors for this indication. **Treatment pathway:** Studies suggest that supportive therapy to rehabilitate erectile function should, ideally, be started as soon as possible following surgery. In the studies, regular PDE5 inhibitor dosing was started at around the time of catheter-removal (7-14 days following surgery) and continued for up to 12 months.

	Initiation will be under specialist supervision in secondary care, with regular follow-up to assess efficacy of treatment.
Summary of evidence/rationale	**Clinical effectiveness:** All three phosphodiesterase-5 (PDE-5) inhibitors have been used successfully post-radical prostatectomy, with greater success following nerve sparing radical prostatectomy. The efficacy of the PDE5 inhibitor depends on preservation of the nerves during surgery; without cyclic guanosine monophosphate (cGMP) there is no substrate for PDE5 to work on (6). Men undergoing bilateral or unilateral prostatectomy have been shown to have a better response to a PDE5 inhibitor than those who had non-nerve-sparing surgery (7; 8; 9). There have been few studies comparing treatment with a PDE5 inhibitor either on-demand or daily versus placebo or a comparator. All the studies are small and of poor quality. In the studies, regular PDE5 inhibitor dosing was started at around the time of catheter-removal (7-14 days following surgery) and continued for up to 12 months. On-demand dosing was used in a few studies, started over 3 months following surgery and mainly assessed after 4-6 doses had been taken. These studies were poorly designed, with no control or placebo groups and no power calculations, or primary endpoints stated (6-9). Regular doses used were sildenafil 25-100mg nightly, sildenafil 100mg three times a week, tadalafil 20mg three times a week and vardenafil 5mg-10mg nightly. Erectile function was assessed using the International Index of Erectile Function (IIEF) and Sexual Encounter Profile (SEP) questions. *IIEF scoring system* 1-7 = severe ED 8-11 = moderate ED 12-16 = mild to moderate ED 17-21 = mild ED Summarised details of the studies are in the following table:

Study authors, year of publication	Sample	Intervention and comparator	Duration of treatment	Outcome
Padma-Nathan et al., 2008(4)	78 men Age not reported	Sildenafil 50mg or 100mg each night vs placebo	36 weeks beginning four weeks after surgery	Normalization of spontaneous erections: Placebo - 4% Sildenafil - 27%
McCullough et al., 2008(10)	54 men (subset of Nathan et al.24) Age range: 38 to 67 years	Sildenafil 50mg or 100mg each night vs placebo	48 weeks beginning post-surgery	Percent responders: placebo – 5% sildenafil 50mg – 24% sildenafil 100mg – 33%
Montorsi et al., 2008(11)	628 men Age 18 to 64 years	On demand vardenafil 5mg to 20mg vs. nightly vardenafil 5mg to 10mg or placebo	9-month double-blind treatment period, a two month single-blind washout period, and an optional two month open-label period with on demand vardenafil. Initiation of treatment within 14 days of surgery	No differences between treatments on the International Index of Erectile Function or sexual completion rates were higher in both vardenafil arms compared to placebo after 9 months of treatment. Percent with IIEF scores ≥ 22: Placebo: 24.8% Vardenafil nightly: 32.0% Vardenafil on demand: 48.2% Positive response for SEP3: Placebo: 25.0% Vardenafil nightly: 34.5% Vardenafil on demand: 45.9%
Montorsi et al. , 2013(12)	423 men Mean age 57.9yrs	Daily tadalafil 5mg vs on demand tadalafil 20mg or placebo	9 months double-blind treatment period followed by a 6-week washout and 3-month open-label tadalafil once	In all groups, IIEF-EF and SEP-3 decreased during washout but continued to improve during open-label treatment. IIEF EF scores ≥22 after washout:

			daily (all patients).	Placebo: 19.1% Tadalafil daily: 20.9% Tadalfil on demand: 16.9%

Safety:
PDE5 inhibitors have been in wide use for many years, and the side effects, precautions and contraindications are well known.

Prior to prescribing, physicians should carefully consider whether their patients with certain underlying conditions (such as cardiac disease) could be adversely affected by the vasodilatory effects of PDE5 inhibitors, especially in combination with sexual activity. Patients with increased susceptibility to vasodilators include those with left ventricular outflow obstruction (e.g., aortic stenosis, hypertrophic obstructive cardiomyopathy), or those with the rare syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure.

Serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension have been reported post-marketing in temporal association with the use of sildenafil. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many events were reported to occur during or shortly after sexual intercourse and a few were reported to occur shortly after the use of a PDE5 inhibitor without sexual activity. It is not possible to determine whether these events are related directly to these factors or to other factors (2).

Cost effectiveness/resource impact:
Generic sildenafil is significantly less expensive than other PDE5 inhibitors.

Equity of access:
This policy is only relevant to men who have undergone radical prostatectomy and consequently require penile rehabilitation to improve erectile function.

References:

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