Q&A 128.3

What is the rationale and evidence for the use of phosphodiesterase-5 inhibitors as supportive therapy to rehabilitate Erectile Function after nerve sparing radical prostatectomy?

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Summary

- Erectile dysfunction (ED) is a common complication following prostatectomy due to cavernosal nerve damage, causing hypoxia, apoptosis, venous leak and fibrosis of the corpora cavernosa.
- Phosphodiesterase – 5 (PDE5) inhibitors promote corporal smooth muscle relaxation and blood flow and early use of these agents following prostatectomy may reverse or minimise these adverse effects.
- All four PDE-5 inhibitors (Avanafil, Sildenafil, Tadalafil, Vardenafil) have been used as supportive therapy to rehabilitate erectile function successfully post-radical prostatectomy, with greater success following nerve sparing radical prostatectomy (NSRP).
- Sildenafil is the most widely studied PDE5 inhibitor for prevention or minimisation of ED following prostatectomy but few trials have studied daily dosing.
- Supportive therapy with PDE5 inhibitors to rehabilitate erectile function should, ideally, be started as soon as possible following surgery. In the studies, regular PDE5 inhibitor dosing was started up to 6 weeks after surgery and continued for up to 12 months. On-demand dosing was used in other studies, with initiation ranging from the day after surgery to over 24 months later.
- Few studies enrolled men after unilateral NSRP; this is associated with a higher risk of losing Erectile Function (EF) completely, compared with bilateral NSRP.
- Both regular (daily or three-times a week) and on-demand (prior to sexual activity) doses were effective but the studies are not designed well enough to draw firm conclusions which regimens offer the best treatment outcomes. There are conflicting results from studies comparing the two treatment regimens possibly due to differences in study designs.
- Treatment should be started early and may need to be continued for 24-36 months to allow full recovery of EF.

Background

Prostate cancer is the most common malignancy in men, making up 26% of all male cancers in England and Wales. The primary curative surgical procedure is a radical prostatectomy (RP) – the total removal of the prostate (1). Erectile dysfunction (ED) is a common complication following a prostatectomy due to cavernosal nerve damage, which can occur even after nerve-sparing surgery (2); a population-based outcomes study showed that 56% of men reported impotence at 18 months or more after surgery (3). Nerve-sparing surgery can be carried out to try to preserve either one or both neurovascular bundles (unilateral or bilateral nerve sparing radical prostatectomy, NSRP) but nerve manipulation during surgery may lead to neuropraxia (nerve injury) (2).

Causes of ED after NRSP include nerve injury, artery injury or deterioration in erection tissue structure and function after surgery. There is growing evidence suggesting use of PDE5 inhibitors after surgery can improve the return of normal erectile function (2). Oral PDE5 inhibitors are licenced for ED and can be prescribed on the NHS for ED post prostatectomy. Currently they are not specifically licensed for supportive therapy to rehabilitate erectile function after NSRP (4). This Q&A reviews the evidence there is to support the use of PDE5 inhibitors as supportive therapy to rehabilitate erectile function following NSRP.

Answer

Corporal veno-occlusive dysfunction (CVOD) is recognised as a major cause of ED following radical prostatectomy. CVOD is as a result of hypoxia, apoptosis, venous leak and an excessive deposition of collagen in the cavernosa following nerve injury (neuropraxia) and rendering the patient unable to obtain and maintain an erection (2;5). Nitric oxide is needed for the production of cGMP in the cavernosa promoting corporal smooth muscle relaxation and blood flow (2;5). PDE5 inhibitors increase cGMPP levels and early therapy can reverse or minimise the effects of CVOD (5). Animal studies have shown that daily administration of a PDE5 inhibitor can prevent CVOD from developing and can normalise the abnormal corporal smooth muscle to collagen ratio that is seen following nerve resection (2).

Recovery of Erectile Function (EF) following radical prostatectomy (RP) can take up to 24 months, but, because lack of oxygenation in the corpus cavernosal can lead to involuntary atrophy due to increasing fibrosis of the smooth muscle, supportive therapy to rehabilitate EF should be started as early as possible (6-8). The focus of therapy for ED following RP is preservation and rehabilitation of EF; one such method is the use of PDE5 inhibitors (6). The efficacy of the PDE5 inhibitor depends on preservation of the nerves during surgery; without cGMP there is no substrate for PDE5 to work on (9). 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 (10-12). Ideally treatment should be started as soon as possible after surgery and it is worth persevering with PDE5 inhibitor therapy for at least 6-9 months because maximal response can take time to achieve. Response rates depend on age, dosage, interval between surgery and starting therapy and degree of cavernous nerve damage. Better long-term results are seen when treatment starts immediately post-operatively; early management of ED prior to penile fibrosis development is important (13).

Studies have compared both on-demand and regular dosing of a PDE5 inhibitor with placebo. No study has directly compared one PDE5 inhibitor to another for this specific indication. Erectile function was assessed using the International Index of Erectile Function (IIEF) and Sexual Encounter Profile (SEP) questions, and scores are detailed in Appendix 1. Different items on the IIEF scale were used in different trials, such as the IIEF-5 (5 questions from the erectile function and intercourse satisfaction domains) or the IIEF-EF (six questions comprising the erectile function domain of the scale). Some studies also included questions from the Sexual Encounter Profile (See Appendix 1). Summarised details of the on-demand studies are included for completeness.

Doses used in the studies are:

- Avanafil 100mg and 200mg on demand*
- Sildenafil 25-100mg nightly
- Sildenafil 50-100mg on-demand*
- Sildenafil 100mg three times a week
- Tadalafil 5mg once daily
- Tadalafil 20mg on-demand*
- Vardenafil 5mg-10mg once a day or at night
- Vardenafil 5-20mg on-demand*

* On-demand doses of sildenafil, tadalafil and vardenafil were taken no more than once a day; for on-demand doses of avanafil, two doses could be taken in 24-hours, at least 12 hours apart [note that the maximum daily dose of avanafil is 200mg].

The recommended dosing of avanafil, sildenafil, tadalafil and vardenafil for the licenced indication is one dose prior to sexual activity; the maximum recommended dosing frequency is once a day (14-17). PDE5 inhibitors can be prescribed on the NHS following prostatectomy for the treatment of erectile dysfunction(18).More than one dose a week can be prescribed if judged clinically appropriate; the daily use of a PDE5 inhibitor would not exceed the licensed recommended doses.

Clinical evidence

Clinical studies are detailed in table 1. There are limitations to many of these studies:

- Study design varied in terms of control groups, with some using placebo and some using no control groups at all.

- Treatment duration varied, ranging from 12 weeks to over a year. Up to 24-36 months of rehabilitation of EF may be required following RP(6).
- Studies also varied in the time following NSRP in which PDE5 inhibitor therapy was started, ranging from 1-14 days to more than 24 months following surgery, which may have impacted on the potential rehabilitative effects, and in the outcome measures used. Early therapy, starting within the first post-operative month or even from the day of catheter removal is recommend to support cavernous oxygenation and prevent otherwise impending fibrosis(7).
- Not all studies included men who had undergone unilateral NSRP, which is associated with a higher risk of losing EF completely, compared with bilateral NSRP(7).
- The use of a washout period after PDE5 inhibitor treatment was used in some studies to determine whether active treatment had greater continued benefits following discontinuation compared with the natural recovery attained with placebo.
- Over 75% of men enrolled in the studies were Caucasian, which may affect generalisability of the results.

Table 1: Clinical studies

Ref	Study design	Drug treatment*	NSRP	ED severity at baseline	Time since surgery (at enrolment)	Primary outcome	Comments
Avanafil							
Mulhall (3)	Randomised, double-blind, placebo-controlled, parallel-group 12-week study (n=298). The study was designed to achieve 86% power with a sample size of 100 men per arm.	Avanafil 100mg (n=99) or 200mg (n=99) or matching placebo (n=100) on-demand (prior to sexual activity, up to 2 doses within 24 hours)	Bilateral	Mild: 9.1% Moderate: 19.5% Severe: 71.5%	6 to ≤12 months: 34.2% 12 to ≤24 months: 40.6% ≥24 months: 25.2%	*Total IIEF-EF score, change from baseline at week 12* +3.6, 100mg, p<0.01 vs. placebo +5.2, 200mg, p<0.01 vs. placebo +0.1, placebo *Changes in SEP-Q2 and SEP-Q3 from baseline at week 12* Changes with avanafil were significantly greater than with placebo (actual changes not stated, p<0.01).	• Short study duration. • Number of avanafil doses taken not stated. • Long time-delay before treatment started. • SEP-Q2 and 3 results only shown pictorially. • Patients who had undergone unilateral NSRP were not evaluated. • More men in the placebo group (24%) discontinued therapy compared with those treated with avanafil (14.1% and 8.1%)
Sildenafil							
Bannowsky (6)	Randomised 52 week study.	Sildenafil 25mg at night (n=23) or no treatment (n=18). Sildenafil 50-100mg on-demand (prior to sexual activity) (see limitations)	Unilateral (n=11) Bilateral (n=32)	Pre-treatment scores (n): IIEF<16: 0 IIEF16-19: 6 IIEF 20-21: 13 IIEF 22-23: 18 IIEF 24-25: 6	7-14 days	*Total IIEF-5 score at week 52* 14.1, treatment group, p<0.001 vs. control 9.3, control group *Erection sufficient for vaginal intercourse, week 52 (potency)* 47%, treatment group 28%, control group *Overall potency* 86%, treatment group (including additional on-demand sildenafil) 66%, control group (including additional on-demand sildenafil)	• Study design is poorly reported and assumption made that it continued for 52 weeks. • It is unclear whether all patients could take on-demand treatment or just those randomised to nightly sildenafil. • Number of patients using on-demand sildenafil not reported. • Nightly vs. on-demand dosing not compared. • The night following catheter removal 95% of men had at least one nocturnal erection, which is not typical of the post-surgical situation in general urological practice

Ref	Study design	Drug treatment	NSRP	ED severity at baseline	Time since surgery (at enrolment)	Primary outcome	Comments
Padma-Nathan (19)	Randomised, double-blind, placebo-controlled study with a 36-week treatment phase and 8 week washout. A sample size of 44 men per group to provide 90% power to detect a significant difference between at least one sildenafil group and placebo	Sildenafil 50mg (n=40), sildenafil 100mg (n=41) or placebo (n=42) at night.	Bilateral	Score of at least 8 for IIEF Q3 and Q4.	4 weeks	82 men completed 36 weeks. 76 men completed 44 weeks (placebo n=25, 50mg n=23, 100mg n=28). *Responders at week 48 (response = score of ≥8 on IIEF Q3 and Q4 plus a 'yes; answer to the question 'over the past 4 weeks have your erections been good enough for satisfactory sexual activity')* 26%, sildenafil 50mg, p=0.04 vs. placebo 29%, sildenafil 100mg, p=0.03 vs. placebo 4%, placebo	• Low overall response rate suggested lack of treatment effect and resulted in stopping enrolment early. • No dose titration or the use of on-demand sildenafil was allowed. • Treatment was started 1 month after surgery, which may have reduced potential rehabilitative effects. • Study was not completed according to original power calculations. • Low response rate may have been due to the stringent definition of response used as the primary outcome or because the treatment time was too short. • Patients who had undergone unilateral NSRP were not evaluated.
Pavlovich (5)	Randomised, double-blind, double-dummy with 12 month treatment period followed by 1 month washout (n=100). The study had >99% power to detect a 5-point difference in the IIEF-EF score at 12 months.	Sildenafil 50mg at night (n=50) or sildenafil 50mg on-demand (prior to sexual activity, max 6/month) (n=50).	Unilateral (n=2) Bilateral (n=98)	Mean pre-treatment IIEF-EF scores of 29.4 (nightly) and 29.3 (on-demand)	1 day	*Total IIEF-EF score at month 13 (following 1 month washout)* 13.8, nightly 19.2, on demand, p=0.022 but p=0.071 when adjusted for nerve sparing score. *Total IIEF-EF score at month 12* 16.7, nightly 18.5, on demand, p=0.456	• No difference in recovery of EF between nightly and on-demand treatment was seen at month 12 and after washout when adjusted for nerve sparing score. • No placebo group was used due to the fact that PDE5 inhibitor use following NSRP was so prevalent the investigators thought that patients would not enrol in case they were randomised to placebo-only treatment. • 50mg dose may be suboptimal but may be better tolerated that 100mg. • 90% were Caucasian: results may not be generalisable.
Feng(10)	Survey after taking at least 4 doses.	Sildenafil 50mg on-demand, prior to sexual activity, flexible dosing (25-100mg) (n=65).	Unilateral (n=15) Bilateral (n=21) Non-NS (n=17)	Pre-op, >75% were potent.	Not stated.	*Response sufficient for intercourse* 71.4%, bilateral, p<0.00001 vs. placebo 80%, unilateral, p<0.00001 vs. placebo 5.9%, non-NS	• Lack of nerve-sparing surgery had a significant impact on the response to sildenafil. • Study is limited by the lack of the following: power calculation; randomisation, number of doses taken; duration of treatment, when treated was started in relation to surgery.

Ref	Study design	Drug treatment	NSRP	ED severity at baseline	Time since surgery (at enrolment)	Primary outcome	Comments
Lowentritt (11)	Open-label study with questionnaire after 8 weeks.	Sildenafil 50mg, increasing to 100mg (n=84). (see comments)	Unilateral (n=19) Bilateral (n=37) Non-NS (n=10)	Mean pre-treatment IIEF-EF scores of 8 (bilateral and non-NS) and 11 (unilateral)	0.3 to 9.5 years (mean 2.1 years)	*Total IIEF-EF score mean change* +8, bilateral +3, unilateral 0, non-NS *IIEF total response, mean change* +15, bilateral +9, unilateral +1, non-NS	• More favourable responses were seen following NSRP than non-NS. • Treatment was started from 0.3 up to 9.5 years after surgery; time since surgery did not have any observable effects. However, by this time potential rehabilitative effects would have been reduced. • Some patients took a higher dose than instructed. Final sildenafil dose was 50mg (n=19), 100mg (n=44), 150mg (n=15) and 200mg (n=6). • Study is limited by lack of details of the following: power calculation; randomisation, number of doses taken, how often doses were taken or whether dosing was regular or on demand.
Tadalafil							
Seo (20)	Retrospective analysis, after robot-assisted laparoscopic radical prostatectomy (n=92).	Tadalafil 5mg at night (n=47) or no tadalafil (n=45).	Unilateral (n=35) Bilateral (n=57)	Mean pre-treatment IIEF-EF scores of 22.7 (tadalafil) and 22.4 (non-tadalafil)	2-3 weeks	*Total IIEF-5 score at 6 months* 10.0, tadalafil vs. 7.0 non-tadalafil *Total IIEF-5 score at 12 months* 13.2, tadalafil vs. 7.7, non-tadalafil *Total IIEF-5 score at 12 months stratified according to surgery* *Bilateral NS:* 15.0 tadalafil vs. 7.8 non-tadalafil, p<0.001 *Unilateral NS:* 10.1 tadalafil vs. 7.5 non-tadalafil, p=0.083 *Positive responders at 1 year* 40%, tadalafil, bilateral 18%, tadalafil, unilateral	• First study assessing long-term use of daily tadalafil following robot-assisted laparoscopic radical prostatectomy. • Small size and retrospective design, with lack of control group. • Lack of detail of what, if any, treated used in the non-tadalafil group. • Positive responders were those whose combined score for IIEF Q2 and Q3 was ≥8.

Ref	Study design	Drug treatment	NSRP	ED severity at baseline	Time since surgery (at enrolment)	Primary outcome	Comments
Montorsi (21)	Randomised, double-blind, placebo-controlled, 12 week study. A sample size of 300 men was calculated to provide 80% power to detect a significant treatment effect.	Tadalafil 20mg (n=201) or placebo (n=102) on-demand prior to sexual activity (maximum once daily).	Bilateral	Mild: 26% Moderate: 22% Severe: 52%	12-24 months: 52% 25-50 months: 48%	*Mean improvement in IIEF-EF score* +5.3, tadalafil, p<0.001 vs. placebo +1.1, placebo *Mean change in SEP-Q2 'yes' responses* +21.6%, tadalafil, p<0.001 vs. placebo +1.9%, placebo *Mean change in SEP-Q3 yes' responses* +23%, tadalafil, p<0.001 vs. placebo +3.7%, placebo	• The study did not evaluate the effects of tadalafil 10mg. • Patients who had undergone unilateral NSRP were not evaluated. • Previous sildenafil users were enrolled but the effects of tadalafil in sildenafil non-responders / failures was not assessed. • Treatment was started 12-50 months after surgery, which may have reduced potential rehabilitative effects.
Montorsi (22)	Randomised, double-blind, double-dummy, placebo-controlled with a 9 month treatment period followed by 6 week drug-free washout and 3 month open-label phase [REACTT study]. A sample size of 412 provided 84% power to detect a 20% difference in the comparisons of tadalafil vs. placebo.	*Double blind phase*: Tadalafil 5mg at night (n=139) or tadalafil 20mg on demand (prior to sexual activity, max 1 dose per day and max 3 per week, n=143) or placebo (n=141). *Drug-free washout*: n=114, 122, 115 respectively. *Open-label phase (tadalafil 5mg once daily)*: n=105, 117, 108 respectively.	Bilateral	Inclusion criterion IIEF-EF ≥22 at least 6 weeks before surgery.	Within 6 weeks	*IIEF-EF score ≥22 after 6 week drug-free washout [primary outcome]* 20.9%, tadalafil nightly 16.9%, tadalafil on demand 19.1%, placebo, p=not significant vs. both tadalafil doses *IIEF-EF score ≥22 at 9 months* 25.2%, tadalafil nightly, p=0.016 vs. placebo 19.7%, tadalafil on demand, p=NS vs. placebo 14.2%, placebo *IIEF-EF score ≥22, open-label phase* 32.4%, tadalafil nightly, p=NS vs. placebo 33.1%, tadalafil on-demand p=NS vs. placebo 27%, placebo	• Primary outcome was not met – tadalafil was not significantly more effective than placebo after the 6 week drug-free washout. Minimal clinically important difference was defined as ≥4 points of change in IIEF-EF. • Double-blind treatment period may have been too short to achieve optimal EF recovery. • After an additional 3 months of open-label tadalafil, none of the comparisons vs. placebo were statistically significant. EF naturally recovers over time, so patients in the placebo group gradually improved during the study. • Only patients undergoing bilateral NSRP were enrolled. • Treatment was started 6 weeks after surgery, which may have reduced potential rehabilitative effects.

Ref	Study design	Drug treatment	NSRP	ED severity at baseline	Time since surgery (at enrolment)	Primary outcome	Comments
Vardenafil							
Bannowsky (7)	Randomised, open-label 12 month study.	Vardenafil 5mg daily (n=12) vs. vardenafil 10mg daily (n=12) vs. control (n=12, no treatment).	Unilateral	Pre-treatment scores (n): IIEF-5 score 19-20: 9 IIEF-5 score 21-22: 12 IIEF-5 score 23-25: 15	After catheter removal.	*IIEF-5 score at 12 months* 13.4, vardenafil 5mg, p<0.01 vs. placebo 12.8, vardenafil 10mg, p<0.01 vs. placebo 8.9, control *Satisfactory vaginal intercourse at 12 months* 50%, vardenafil 5mg 42%, vardenafil 10mg 20%, control	• No significant difference in treatment effect was seen between the two vardenafil doses. • Unilateral NSRP is associated with a higher risk of losing EF completely, compared with bilateral NSRP. • Study was not blinded and had no placebo group.
Montorsi (23)	Randomised, double-blind, double-dummy, placebo-controlled with a 9 month treatment period followed by 2 month washout and 2month open-label phase.	Vardenafil 10mg nightly (decreasing to 5mg if required, n=210) or vardenafil 10mg on demand (titrating to 5 or 20mg if required, n=208) or placebo (n=210).	Bilateral	Pre-treatment IIEF-EF score ≥26.	Within 14 days	*IIEF-EF score ≥22 after 6 week drug-free washout [primary outcome]* 24.1%, vardenafil nightly 29.1%, vardenafil on demand 28.9%, placebo *IIEF-EF score ≥22 after 9 months [last observation carried forward, LOCF]* 32%, vardenafil nightly 48.2%, vardenafil on demand, p=0.0001 vs. placebo, p=0.0065 vs. vardenafil nightly 24.8%, placebo *IIEF-EF score ≥26 after 9 months [LOCF]* 20.1%, vardenafil nightly 36.2%, vardenafil on-demand 16.8%, placebo, p=0.0003 vardenafil vs. placebo	• Two-thirds (67%) completed the study. • The primary outcome was not met - responses after the drug washout were similar between vardenafil and placebo and. A 9 month treatment period may not have been long enough to achieve optimal EF recovery. • On-demand treatment was of greater benefit that nightly treatment. • No maximum number of on demand doses was stated. • Participant-controlled dose adjustment could have muddied the results. • Use of LOCF data assumes that the patient clinical situation does not improve / worsen by endpoint. • 95% of the men had nocturnal erections following catheter removal, which is not typical of the post-surgical situation in general urological practice.

Limitations

- Few studies have evaluated daily dosing of PDE5 inhibitors and not all are well designed or have control groups.
- Most studies were up to one year duration, which is less than the estimated 24-36 months required for penile rehabilitation.
- Initiation of treatment varied from the day after surgery to weeks to months later, thereby potentially reducing rehabilitative effects and could explain differences seen between studies.
- Outcome measures varied between the studies.
- No studies have compared shorter acting and longer acting PDE5 inhibitors.

References

(1) NICE CG175 Prostate cancer: diagnosis and treatment. Full guideline. January 2014 National Collaborating Centre for Cancer http://www.nice.org.uk/guidance/cg175/resources/cg175-prostate-cancer-full-guideline3

(2) Rambhatla A, Kovanecz I, Ferrini M et al. Rationale for phosphodiesterase 5 inhibitor use post-radical prostatectomy: experimental and clinical review. Int J Impot Res 2008; 20:30-34.

(3) Mulhall JP, Burnett AL, Wang R et al. A phase 3, placebo controlled study of the safety and efficacy of avanafil for the treatment of erectile dysfunction after nerve sparing radical prostatectomy. J Urol 2013; 189:2229-2236.

(4) Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press <http://www.medicinescomplete.com> [Accessed on date:16/05/2016]

(5) Pavlovich CP, Levinson AW, Su L-M et al. Nightly vs. on-demand sildenafil for penile rehabilitation after minimally invasive nerve-sparing radical prostatectomy: results of a randomized double-blind trial with placebo. BJU Int 2013; 112:844-851.

(6) Bannowsky A, Schulze H, van der Horst C et al. Recovery of erectile function after nerve-sparing radical prostatectomy: improvement with nightly low-dose sildenafil. BJU Int 2008; 101:1279-1283.

(7) Bannowsky A, van Ahlen H, Loch T. Increasing the dose of vardenafil on a daily basis does not improve erectile function after unilateral nerve sparing radical prostatectomy. J Sex Med 2012; 9:1448-1453.

(8) Glina S. Erectile dysfunction after radical prostatectomy. Drugs & Aging 2011; 28(4):257-266.

(9) Raina R, Lakin MM, Agarwal A et al. Long-term effect of sildenafil citrate on erectile dysfunction after radical prostatectomy: 3-year follow-up. Urology 2003; 62(1):110-115.

(10) Feng MI, Huang S, Kaptein J et al. Effect of sildenafil citrate on post-radical prostatectomy erectile dysfunction. J Urol 2000; 164:1935-1938.

(11) Lowentritt BH, Scardino PT, Miles BJ et al. Sildenafil citrate after radical retropubic prostatectomy. J Urol 1999; 162:1614-1617.

(12) Zippe CD, Jhaveri FM, Klein EA et al. Role of Viagra after radical prostatectomy. Urology 2000; 55:241-245.

(13) Kirby MG, White ID, Butcher J et al. Development of UK recommendations on treatment for post-surgical erectile dysfunction. Int J Clin Pract 2014; 68(5):590-608.

(14) Summary of Product Characteristics. Spedra 50mg, 100mg and 200mg tablets. Date of revision of the text: 10/03/2016. A.Menarini Farmaceutica Internazionale. Accessed via: www.emc.medicines.org.uk. on 16/05/2016.

(15) Summary of Product Characteristics. Viagra 25mg, 50mg, 100mg. Date of revision of the text: 10/2015. Pfizer Ltd Accessed via: www.emc.medicines.org.uk. on 16/05/2016.

(16) Summary of Product Characteristics. Cialias 2.5mg, 5mg, 10mg & 20mg film-coated tablets. Date of revision of the text: 03/05/2016. Eli Lilly and Company Limited. Accessed via: www.emc.medicines.org.uk. on 16/05/2016.

(17) Summary of Product Characteristics. Levitra 5mg, 10mg, 20mg film-coated tablets. Date of revision of the text: 12/2015. Bayer PLC. Accessed via: www.emc.medicines.org.uk. on 16/05/2016.

(18) Drug Tariff. November 2016. NHS business Service Authority. Accessed via: <http://www.nhsbsa.nhs.uk/PrescriptionServices/4940.aspx> on 02/11/2016

(19) Padma-Nathan H, McCullough AR, Levine LA et al. Randomized, double-blind, placebo-controlled study of postoperative nightly sildenafil citrate for the prevention of erectile dysfunction after bilateral nerve-sparing radical prostatectomy. Int J Impot Res 2008; 20:479-486.

(20) Seo YE, Kim SD, Kim TH et al. The efficacy and safety of tadalafil 5mg once daily in the treatment of erectile dysfunction after robot-assisted laparoscopic radical prostatectomy: 1-year follow-up. Korean J Urol 2014; 55:112-119.

(21) Montorsi F, Padma-Nathan H, McCullough A et al. Tadalafil in the treatment of erectile dysfunction following bilateral nerve sparing radical retropubic prostatectomy: a randomized, double-blind, placebo-controlled trial. J Urol 2004; 172(3):1036-1041.

(22) Montorsi F, Brock G, Stolzenburg J-U et al. Effects of tadalafil treatment on erectile function recovery following bilateral nerve-sparing radical prostatectomy: a randomised placebo-controlled study (REACTT). Eur Urol 2014; 65:587-596.

(23) Montorsi F, Brock G, Lee J et al. Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. Eur Urol 2008; 54:924-931.

(24) Tsertsvadze A, Yazdi A, Fink HA et al. Appendix H. Instruments Used in the Assessment of Treatment Outcomes. Diagnosis and Treatment of Erectile Dysfunction. Evidence Reports/Technology Assessments, No. 171. Rockville, MD.: Agency for Healthcare Research and Quality (US), 2009.

(25) Sexual health inventory for men. Accessed 16/05/2016. http://www.njurology.com/_forms/shim.pdf

Quality Assurance

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Search strategy

- Embase: [SILDENAFIL/ OR SILDENAFIL NITRATE/ OR TADALAFIL/ OR VARDENAFIL/ OR AVANAFIL] AND exp PROSTATECTOMY/ [Limit to: Human and English Language and Publication Year 2014-2016]
- Medline : PHOSPHODIESTERASE 5 INHIBITORS/ AND PROSTATECTOMY/ [Limit to: Publication Year 2014-2016 and (Language English)]
- Medline: [SILDENAFIL CITRATE/ OR TADALAFIL/ OR VARDENAFIL DIHYDROCHLORIDE/] AND PROSTATECTOMY/ [Limit to: Publication Year 2014-2016 and (Language English)]
- Medline: PROSTATECTOMY AND (avanafil).ti,ab
- Cochrane Library
- NHS Evidence : Erectile Dysfunction and prostatectomy
- New Drugs Online
- Martindale

Appendix 1:

Sexual Encounter Profile (SEP)(22;24)

SEP-Q1: Were you able to achieve at least some erection [mean rate per patient]
SEP-Q2: Were you able to insert your penis into your partner's vagina?
SEP-Q3: Did your erection last long enough for you to have successful intercourse?
SEP-Q4: Were you satisfied with the hardness of your erection?
SEP-Q5: Were you satisfied with this sexual experience?
Responses: yes or no.

IIEF scoring system(24)

The green shading highlights those questions in the Erectile Function domain of the IIEF.
The blue shaded questions are those in the shorter IIEF-5 questionnaire, which are also in the Sexual Health Inventory for Men (SHIM) (25). The SHIM further classifies ED severity with the following breakpoints:

1-7 = severe ED
8-11 = moderate ED
12-16 = mild to moderate ED
17-21 = mild ED

	Table 1	**Score**					
Domain	**Over the past 4 weeks:**	**0**	**1**	**2**	**3**	**4**	**5**
EF	(1) How often were you able to get an erection during sexual activity?	No sexual activity	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
EF	(2) When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Did not attempt intercourse	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
EF	(3) When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?	Did not attempt intercourse	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
EF	(4) During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Did not attempt intercourse	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
EF	(5) During sexual intercourse how difficult was it to maintain your erection to the completion of intercourse?	Did not attempt intercourse	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
IS	(6) How many times have you attempted sexual intercourse?	No attempts	1 to 2 attempts	3 to 4 attempts	5 to 6 attempts	7 to 10 attempts	11+ attempts

IS	(7) When you attempted sexual intercourse, how often was it satisfactory for you?	Did not attempt intercourse	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
IS	(8) How much have you enjoyed sexual intercourse?	No intercourse	No enjoyment	Not very enjoyable	Fairly enjoyable	Highly enjoyable	Very highly enjoyable
OF	(9) When you had sexual stimulation or intercourse, how often did you ejaculate?	No sexual stimulation / intercourse	Almost never / never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
OF	(10) When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?	No sexual stimulation / intercourse	Almost never / never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
SD	(11) How often have you felt sexual desire?	-	Almost never / never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
SD	(12) How would you rate your level of sexual desire?	-	Very low / none at all	Low	Moderate	High	Very high
OS	(13) How satisfied have you been with your overall sex life?		Very dissatisfied	Moderately dissatisfied	About equally satisfied and dissatisfied	Moderately satisfied	Very satisfied
OS	(14) How satisfied have you been with your sexual relationship with your partner?		Very dissatisfied	Moderately dissatisfied	About equally satisfied and dissatisfied	Moderately satisfied	Very satisfied
EF	(15) How do you rate your confidence that you could get and keep an erection?	-	Very low	Low	Moderate	High	Very high

Domain	**Minimum / maximum score**
EF: erectile function	1 / 30
OF: orgasmic function	0 / 10
SD: sexual desire	2 / 10
IS: intercourse satisfaction	0 / 15
OS: Overall satisfaction	2 / 10