PrescQIPP Community Interest Company

Tadalafil once daily (Cialis® once-a-day)

This is one of a number of bulletins providing further information on medicines contained in the PrescQIPP DROP-List (Drugs to Review for Optimised Prescribing). This bulletin focuses on tadalafil once daily. It provides the rationale for new patients to be started on generic sildenafil on demand for erectile dysfunction (ED). It also recommends switching current patients to generic sildenafil on demand for ED, where clinically appropriate. Information on adverse effects and options for dose conversion in support of the switch and potential switch savings are provided. Further bulletins, including the DROP-List,[1] are available on the PrescQIPP website, www.prescqipp.info

Recommendations

Erectile dysfunction

- Choose the PDE5 inhibitor with the lowest acquisition cost (currently generic sildenafil), unless it is clinically unsuitable. The evidence suggests that sildenafil, tadalafil and vardenafil have similar efficacy in treating ED.
- Do not choose tadalafil once daily for treating ED on the basis of favourable efficacy. The evidence suggests that tadalafil 5mg daily has a similar efficacy to tadalafil 10mg or 20mg taken on demand for ED.
- Consider switching to generic sildenafil for men receiving other PDE5 inhibitors (including tadalafil once daily), where clinically appropriate.
- For many men with ED taking tadalafil once daily may increase tadalafil exposure. The product information for Cialis® only supports consideration of daily dosing in men who anticipate frequent use (at least twice weekly). It advises periodic reassessment of the appropriateness of continued daily use.

Use after radical prostatectomy

- Men with prostate cancer should have early and ongoing access to specialist ED services. Those who experience loss of erectile function should be offered PDE5 inhibitors to improve their chance of spontaneous erections, in line with NICE guidance.
- All of the available PDE5 inhibitors are licensed for treating ED and can be prescribed on an NHS prescription after prostatectomy. None however are specifically licensed for prevention of long term ED or penile rehabilitation after prostatectomy.
- There is a good rationale for the use of PDE5 inhibitors for penile rehabilitation after radical prostatectomy, based on scientific theory and preclinical evidence. However, the clinical evidence is limited and conflicting.
- In the absence of robust evidence favouring a particular treatment regimen, local policy makers may advocate choosing the drug with the lowest acquisition cost (currently generic sildenafil), where clinically appropriate. Consultation with local stakeholders including urology specialists is needed.
- Organisations considering a review of prescribing should ensure that the process and switching methodology is agreed locally by all key stakeholders including GPs, urology specialists and other relevant health professionals.
- Whilst the clinical evidence supporting a rehabilitative effect (continued benefit following drug discontinuation) of PDE5 inhibitors after prostatectomy is discouraging, several studies have shown PDE5 inhibitors to be effective at improving drug-assisted erectile function after prostatectomy.

Signs and symptoms of benign prostatic hyperplasia

- Review the treatment of men receiving a PDE5 inhibitor solely for the purpose of treating lower urinary tract symptoms (only tadalafil 5mg daily is licensed), unless use is part of a randomised controlled trial, in accordance with NICE guidance.

Background

The PrescQIPP DROP-List is an accumulation of medicines that are regarded as low priority, poor value for money or medicines for which there are safer alternatives. The DROP-List also includes medicines that could be considered for self care with the support of the community pharmacist. Tadalafil once daily features on the DROP-List as an item that is poor value for money compared with available alternatives.

Rationale for restricting or avoiding once daily tadalafil

Erectile dysfunction and other indications for PDE-5 inhibitors

Four phosphodiesteradse-5 (PDE5) inhibitors are licensed in the UK: sildenafil, tadalafil, vardenafil and avanafil. All are licensed for the treatment of ED,[2-5] which has been defined as the persistent inability to attain and/or maintain an erection sufficient for sexual performance.[6] Erectile dysfunction is a very common disorder with a prevalence that increases steeply with age.[7] The treatment of ED depends on its cause, with PDE5 inhibitors being a first line treatment where pharmacotherapy is indicated.[6,7] PrescQIPP bulletin 73 on 'Male sexual dysfunction: Management of erectile dysfunction and premature ejaculation' discusses the general use of PDE5 inhibitors in treating ED and makes recommendations regarding their prescribing in primary care. This bulletin focuses specifically on the use of PDE5 inhibitors for indications in which tadalafil once daily might be considered.

Tadalafil has a half-life of 17.5 hours, approximately four times longer than sildenafil or vardenafil. It has been found to be suitable for once daily administration, with steady state being reached after approximately five days.[8] Neither sildenafil, vardenafil nor avanafil are licensed for continuous daily administration; for ED they should be taken on demand, prior to sexual activity, up to once a day.[2,4,5] Even where they are taken on a daily basis their different pharmacokinetic characteristics mean that regular once daily dosing may be insufficient to reach steady state. For example, sildenafil is also licensed for pulmonary artery hypertension, a condition in which a more continuous drug effect is needed. For this indication sildenafil (as Revatio®) is given three times a day.[9]

Tadalafil once daily (Cialis® 2.5mg and 5 mg tablets) is licensed for ED in adult males. The product information states that in men who anticipate a frequent use of tadalafil (i.e. at least twice weekly) a once daily regimen with the lowest doses of tadalafil might be considered suitable, based on patient choice and the physician's judgement.[3] This gives a potential advantage in that ED therapy could be taken without regard to timing of sexual activity, but conversely it does promote continuous use of a medication where it may not be necessary. The 5mg daily dose of tadalafil is also licensed for benign prostatic hyperplasia in adult men.[3]

PDE5 inhibitors have also been used with the aim of preserving and rehabilitating erectile function after radical prostatectomy for prostate cancer.[10] ED is a common complication after radical prostatectomy experienced by 25-75% of men.[7] The main pathophysiological mechanism behind this is considered to be damage to the cavernosal nerves, which can be affected even after nerve-sparing surgery.[10,11] This has led to the development of penile rehabilitation programmes, often using PDE5 inhibitors (including tadalafil), which aim to improve long-term erectile function after nerve-sparing surgery.[11] The intention is to promote re-oxygenation of the tissue in order to maximise the potential for cavernosal nerve repair and reduce penile fibrosis.[12] None of the available PDE5 inhibitors are specifically licensed for prevention of long term ED or penile rehabilitation after prostatectomy.[2-5]

The use of PDE5 inhibitors for the treatment of pulmonary arterial hypertension is not within the scope of this bulletin.

National guidance

Erectile dysfunction

Since 1998 the provision of PDE5 inhibitors on NHS prescriptions has been subject to certain restrictions.[13,14] In 2014 the regulations were amended to remove the requirement for prescribers to restrict NHS prescribing of generic sildenafil to men with ED who meet defined criteria. Changes were also made to how those with severe distress can access treatment. The changes include the following:

- Generic sildenafil tablets can be prescribed on the NHS for any person with ED, regardless of cause.
- The other PDE5 inhibitors - branded sildenafil (e.g. Viagra®), vardenafil, tadalafil and avanafil can only be prescribed for those who meet NHS criteria*. If a person does not meet these criteria, a private prescription can be offered.
- Those who suffer severe distress as a result of ED can be treated in primary care.

*See PrescQIPP bulletin 73 on Male sexual dysfunction: Management of erectile dysfunction and premature ejaculation for the list of NHS criteria and for information about how the changes to prescribing regulations affects other ED treatments.

The changes were made following a significant reduction in the price of sildenafil after the expiry of patent protection for Viagra® in 2014. The restrictions continue to apply to branded Viagra® and certain other ED therapies such as alprostadil, avanafil, tadalafil and vardenafil.

Advice around the quantity of medication to prescribe remains unchanged at one treatment per week, based on research evidence in the 40-60 year age group. The prescribing doctor can prescribe more than one dose a week if it is considered clinically appropriate.[13]

NICE has not published a clinical guideline on the management of ED, although several NICE guidelines make recommendations about identifying and managing ED in specific patient groups. NICE guidance states that, unless contraindicated, PDE5 inhibitors should be offered to men with ED and type 1 diabetes (NG17) or type 2 diabetes (NG28), or men who have had a myocardial infarction more than six months earlier who are now stable (CG172).[15-17]

NICE guidance on the diagnosis and management of men with prostate cancer (CG175) states that they should have early and ongoing access to specialist ED services. Further, it states that men with prostate cancer who experience loss of erectile function should be offered PDE5 inhibitors to improve their chance of spontaneous erections.[18]

None of the NICE guidelines above discuss choice of PDE5 inhibitor or dosage regimens, other than to recommend that the PDE5 inhibitor with the lowest acquisition cost should be chosen (which is stated in both the type 1 and type 2 diabetes guidelines).[15,16] Generic sildenafil is currently the lowest cost PDE5 inhibitor by a considerable margin (see costs section, page 7).

Guidelines on the management of ED from the British Society for Sexual Medicine recommend PDE5 inhibitors as a first-line treatment due to their proven efficacy and safety both in non-selected populations of men with ED and in specific sub-groups (e.g. men with diabetes and those who have had a prostatectomy).[6] The guideline notes that tadalafil is licensed for daily use at 2.5mg and 5mg for those who anticipate sexual activity more than twice per week. It states that this regimen may be more cost effective in such cases, however the availability of generic sildenafil means that this is no longer the case when all PDE5 inhibitors are considered.

European guidelines on the management of male sexual dysfunction also recommend first-line use of PDE5 inhibitors for ED. They note the availability of tadalafil once daily as an alternative to on-demand dosing of tadalafil for couples who prefer spontaneous rather than scheduled sexual activities or who anticipate frequent sexual activity, with the advantage that dosing and sexual activity no longer need to be temporally linked. They advise periodic reassessment of the appropriateness of the continuous use of a daily regimen.[7]

In 2009 the Scottish Medicines Consortium (SMC) accepted tadalafil 2.5mg and 5mg tablets for use in NHS Scotland for regular once daily administration in patients with ED responding to an on demand regimen of tadalafil who anticipate frequent use (at least twice weekly). They stated that at this level of on-demand use, the low dose regular regimen would be expected to be cost-neutral overall. The SMC also stated that tadalafil represents an alternative to other PDE5 inhibitors, primarily for patients for whom the longer duration of action represents a significant advantage.[19] Since this decision was made, sildenafil has become available generically at a greatly reduced cost. Present-day price comparisons of different PDE5 inhibitor options must therefore take this into consideration (see cost section, page 7).

Prevention of long-term ED or penile rehabilitation after prostatectomy

NICE guidance states that men with prostate cancer who experience loss of erectile function should be offered PDE5 inhibitors to improve their chance of spontaneous erections.[18] The need for further research into the timing and effectiveness of treatments for ED after all treatments for prostate cancer is highlighted.[20] A European Guideline on male sexual dysfunction also advocates the use of PDE5 inhibitors for ED after radical prostatectomy, as do guidelines published by expert groups in the UK.[6,7,12,21]

Guidelines on ED published by a UK expert group in 2008 stated that early introduction of pharmacotherapy may improve the rate of recovery of normal erectile function after nerve-sparing prostatectomy. They went on to say that rehabilitation programmes for men after radical prostatectomy may offer the prospect of a 'cure' for ED, but that at the time of writing the efficacy of such programmes were unproven.[21] A more recent version of the guideline published in 2013 does not specifically discuss the use of PDE5 inhibitors for rehabilitation purposes after prostatectomy.[6]

Benign prostatic hyperplasia

Tadalafil 5mg once daily is the only PDE5 inhibitor licensed for treating the signs and symptoms of benign prostatic hyperplasia.[3] NICE guidance on the management of lower urinary tract symptoms (LUTS) in men (CG97) states that PDE5 inhibitors should not be offered solely for the purpose of treating lower urinary tract symptoms in men, except as part of a randomised controlled trial. The current evidence for PDE5 inhibitors in this indication includes men with LUTS and ED. Therefore the standing Committee that updated the guideline in 2015 decided that it was not appropriate to make a recommendation about the routine use of PDE5 inhibitors in clinical practice. They stated that more evidence is needed to enable a recommendation to be made on the use of PDE5 inhibitors in all men with LUTS, including those without ED.[22] Furthermore, a NICE Technology Appraisal on the use of tadalafil for the treatment of symptoms associated with benign prostatic hyperplasia was terminated in 2013 due to non-submission of supporting evidence from the manufacturer.[23] Use of daily tadalafil for this indication is therefore not considered further here.

Clinical effectiveness

Erectile dysfunction

Randomised placebo-controlled trials of individual PDE5 inhibitors have shown them to be effective interventions for ED.[24,25] The paucity of meaningful head-to-head trials of PDE5 inhibitors in ED makes assessment of comparative efficacy difficult. Data from four systematic reviews with meta-analysis are available.[26-29] They compare mostly placebo-controlled trials, although two systematic reviews included a small number of head-to-head trials. In general the data have suggested similar efficacy for sildenafil, tadalafil and vardenafil. However two of the systematic reviews include suggestions of greater efficacy with some pairwise comparisons.[27,29] Such suggestions should be interpreted cautiously due to limitations of the data, and in the absence of good quality comparative trials.[27,30,31]

To support the hypothesis that low dose, once daily tadalafil may be a safe and effective treatment in the general ED population, initial randomised placebo-controlled trials investigating tadalafil 2.5mg and 5mg daily versus placebo (n=287, 24 weeks), and 5mg and 10mg daily versus placebo (n=268, 12 weeks) were undertaken.[8] A third study (n=298, 12 weeks) exclusively enrolled men with type 1 or type 2 diabetes and randomised them to treatment with tadalafil 2.5mg or 5mg daily or placebo.[32] The primary efficacy

end points were the International Index of Erectile Function (erectile function domain) (IIEF-EF) to assess the severity, and the number of 'yes' responses to the Sexual Encounter Profile (SEP) Questions 2 (successful penetration) and 3 (successful intercourse). Exclusion criteria included non-response to PDE5 inhibitors, cardiac disease and current nitrate use. In all studies tadalafil significantly and clinically improved erectile function as measured by the three primary efficacy measures.[32] It has been noted that the efficacy associated with once daily tadalafil 5mg in the studies with a mixed population (rather than exclusively men with diabetes) was consistent with those of historical on demand studies evaluating tadalafil 10 and 20 mg.[8] Head-to-head comparisons of on demand and once daily therapies were not conducted in these studies, and are needed to confirm such observations.

Since the publication of these initial once daily tadalafil studies, further studies have been published, but there is still a lack of robust head-to-head data comparing on demand tadalafil treatment with a daily dose of 2.5mg or 5mg of tadalafil in the general ED population.

Use after radical prostatectomy

There are a number of recent reviews on the subject of PDE5 inhibitor use after radical prostatectomy, as well as a UKMi Medicines Q&A on the subject.[10,33-35] The studies included vary from those investigating the effect of PDE5 inhibitors on drug-assisted erectile function (i.e. efficacy during the treatment period), to studies that assessed erectile function after a drug-free washout period to see if there was a continued benefit following discontinuation compared with the natural recovery attained with placebo (i.e. investigating rehabilitative effects).

The UKMi Medicines Q&A summarises the findings of 11 studies of PDE5 inhibitors after prostatectomy (one avanafil, five sildenafil, three tadalafil and two vardenafil. See UKMi document for a summary of the studies). Study design varied with most comparing either on demand or regular dosing of a PDE5 inhibitor with placebo (or untreated control). Treatment duration varied and ranged from 12 weeks to over a year, and there were differences in the lapse of time between surgery and the initiation of the PDE5 inhibitor. The UKMi Q&A notes that for rehabilitative purposes treatment periods of up to 24-36 months may be needed, and that there is a good rationale for preferring early initiation of supportive therapy. The type of radical prostatectomy that people had undergone also varied between studies; bilateral nerve-sparing surgery gives the best outcomes for erectile function.

Of the 11 studies included in the UKMi Q&A, three placebo-controlled studies assessed treatment efficacy after a drug-free washout period. None provided compelling evidence to support a continued treatment effect; one small study (n=123) did demonstrate an increased return of spontaneous erections with sildenafil compared with placebo after an eight week washout period, but the study stopped enrollment early as the low overall response rate suggested lack of treatment effect.[10,35] Two larger studies (n=423 investigating tadalafil and n=628 investigating vardenafil) failed to show a statistically significant difference in erectile function between active treatment or placebo groups after the washout period.[10,36,37] These findings could have been negatively influenced by study design, for example the duration of the studies or the interval between surgery and treatment initiation may not have been optimal for demonstrating a rehabilitative effect. However, it is also possible that the results were negative because PDE5 inhibitors do not have a continued positive effect on erectile function beyond the treatment period, after radical prostatectomy.

It should be noted that whilst the clinical evidence supporting a rehabilitative effect of PDE5 inhibitors after prostatectomy is discouraging, several studies have shown PDE5 inhibitors to be a successful treatment for ED after prostatectomy.[10,24,38] Indeed, some of the studies that failed to show a sustained benefit of PDE5 inhibitor after a washout period provided evidence of improved erectile function during the treatment period.[36,37]

One such study, the REACTT study, is of particular interest as it investigated tadalafil and compared both daily and on demand dosing to placebo.[36] The primary objective was to compare the efficacy of tadalafil 5mg once daily and tadalafil 20mg on demand versus placebo taken over nine months in improving unassisted erectile function following nerve-sparing radical prostatectomy, as measured by the proportion of men achieving an IIEF-EF score ≥22 after a six week drug-free washout. A further

three months of open-label treatment with tadalafil once daily was then given. As already discussed, no statistically significant difference was found between either active treatment group and placebo for the primary objective (IIEF-EF score ≥22 after the six week washout). When IIEF-EF score ≥22 was assessed at nine months (i.e. on treatment before the six week washout, a secondary outcome measure) a statistically significant difference was demonstrated in the tadalafil once daily versus placebo comparison, but not in the tadalafil on demand vs. placebo comparison. Some of the other secondary outcomes and some post-hoc analysis of the data also favoured tadalafil once daily, and the authors concluded that tadalafil once daily was most effective for drug-assisted erectile function in men with ED following nerve-sparing radical prostatectomy.[36] It should be borne in mind however that drug-assisted erectile function was not the primary outcome of this study; an earlier study by the same principal investigator for which the primary outcome was drug-assisted erectile function found tadalafil taken on demand to be an effective treatment for ED after radical prostatectomy.[39] At the end of the additional three month open-label daily tadalafil stage none of the comparisons versus placebo were statistically significant.[36]

Several reviews on the subject of PDE5 inhibitors for penile rehabilitation have noted that whilst the scientific theory and preclinical evidences support the rationale, the clinical evidence is limited and conflicting. Further study is required to establish the optimal penile rehabilitation program.[11,33,34]

Evidence summary

- PDE5 inhibitors are an effective intervention for ED.[24,25]
- Data suggests that sildenafil, tadalafil and vardenafil have similar efficacy in treating ED, but there is a lack of robust comparative trials to confirm this.[26-29]
- Data suggests that tadalafil 5mg daily has a similar efficacy to tadalafil 10mg or 20mg given on demand.[8] However there is a lack of head-to-head data in the general ED population to confirm this.
- There is a good rationale for the use of PDE5 inhibitors for penile rehabilitation after radical prostatectomy, based on scientific theory and preclinical evidence. However the clinical evidence is limited and conflicting.[11,33,34]
- One small study of sildenafil versus placebo after nerve-sparing radical prostatectomy did demonstrate a continued difference favouring sildenafil after an eight week washout period, but two larger studies (investigating tadalafil and vardenafil) did not demonstrate a difference after the washout period.[10,35-37]
- Whist the clinical evidence supporting a rehabilitative effect of PDE5 inhibitors after prostatectomy is discouraging, several studies have shown PDE5 inhibitors to be effective at improving drug-assisted erectile function after prostatectomy.[10,24,38]

Safety

The most common side-effects of PDE5 inhibitors are headache, flushing, dyspepsia, nasal congestion, visual disturbance and myalgia. Visual disturbances are almost exclusively associated with sildenafil, and back pain with tadalafil. Although serious side-effects appear to be rare, they have been reported and include nonarteritic ischemic optic neuritis, which may result in irreversible blindness.[40] All PDE5 inhibitors are therefore contraindicated in people who have loss of vision in one eye. Other contraindications include men taking nitrates or nitric oxide donors, and men with cardiac disease for whom sexual activity is inadvisable (consider the potential cardiac risk of sexual activity in men with pre-existing cardiovascular disease).[2-5]

Considering tadalafil once daily specifically, its safety profile has been evaluated in the one and two year open-label extension periods of studies of daily tadalafil in the general ED population. Compared with adverse events reported in trials of on demand dosing of tadalafil, there was no evidence of increased incidence of or any new or unexpected adverse events over this time period.[8]

Pharmacokinetic studies have shown that for men taking at least two doses per week of tadalafil 20mg, their cumulative weekly exposure is similar to that in men receiving tadalafil 5mg once daily.[8] Research suggests that the average frequency of sexual intercourse in the 40-60 age range is once a week.[13] Therefore for many men with ED the use of daily tadalafil could represent an increase in tadalafil exposure. The product information for Cialis® only supports consideration of daily dosing in men who anticipate frequent use (at least twice weekly). It advises periodically reassessing the appropriateness of continued daily use. Daily dosing is not recommended in those with severe renal impairment due to increased exposure.[3]

Tadalafil is principally metabolised by CYP3A4, so caution is needed where people are taking other drugs that affect this enzyme.[3]

Costs

There is a significant difference in cost between tadalafil once daily and other available PDE5 inhibitors, particularly generic sildenafil. Table 1 below illustrates the costs.

Table 1. PDE5 inhibitor costs per month based on four doses per month or 28 doses of tadalafil 2.5mg and 5mg once daily[41,42]

PDE5 inhibitor	Cost per 28 days based on four doses a month or once daily dosing of tadalafil
tadalafil 2.5mg/5mg daily dose (Cialis®)	£54.99
tadalafil 10mg/20mg (Cialis®)	£28.88
sildenafil 25mg (generic)	£0.92
sildenafil 50mg (generic)	£1.01
sildenafil 100mg (generic)	£1.12
Nipatra® (sildenafil) 25mg chewable tablets	£13.72
Nipatra® (sildenafil) 50mg chewable tablets	£17.02
Nipatra® (sildenafil) 100mg chewable tablets	£18.80
Viagra® (sildenafil) 25mg tablets	£16.59
Viagra® (sildenafil) 50mg tablets	£21.27
Viagra® (sildenafil) 100mg tablets	£23.50
vardenafil 5mg (Levitra®)	£7.56
vardenafil 10mg (Levitra®)	£14.08
vardenafil 20mg (Levitra®)	£23.48
vardenafil orodispersible tablet (ODT) 10mg (Levitra®)	£17.88
avanafil 50mg (Spedra®)	£10.94
avanafil 100mg (Spedra®)	£14.08
avanafil 200mg (Spedra®)	£21.90

Prescribing review and switching options

Local policy should outline which PDE5 inhibitors should be prescribed in each CCG and the indications for which they can (and cannot) be prescribed. For unlicensed indications, such as penile rehabilitation after prostatectomy, consideration as to who initiates, continues and reviews treatment is also needed.

For erectile dysfunction:

- New patients should be commenced on the PDE5 inhibitor with the lowest acquisition cost (currently generic sildenafil) unless it is clinically unsuitable.

- Consider switching to generic sildenafil for men receiving other PDE5 inhibitors (including tadalafil once daily), where clinically appropriate. See PrescQIPP bulletin 73 on 'Male sexual dysfunction: Management of erectile dysfunction and premature ejaculation' and associated resources for an audit on PDE5 inhibitors. https://www.prescqipp.info/resources/category/145-male-sexual-dysfunction
- The lack of head-to-head studies means that a pragmatic approach to choosing comparable doses will be needed when switching. Unless a lower starting dose is indicated, prescribers may prefer to switch to sildenafil 50mg. Titrate the dose up or down according to the response and tolerability, in accordance with the product information for sildenafil.[43]

Other indications:

- For penile rehabilitation after prostatectomy, the clinical evidence is limited and conflicting. In the absence of robust evidence favouring a particular treatment regimen, local policy makers may advocate choosing the drug with the lowest acquisition cost (currently generic sildenafil), where clinically appropriate. Consultation with local stakeholders including urology specialists is needed.
- Organisations considering a review of prescribing should ensure that the process and switching methodology is agreed locally by all key stakeholders including GPs, urology specialists and other relevant health professionals.
- Review the treatment of men receiving a PDE5 inhibitor solely for the purpose of treating LUTS (only tadalafil 5mg daily is licensed), unless it is as part of a randomised controlled trial.

Savings

There is a significant difference in cost between tadalafil once daily (Cialis® 2.5 mg and 5 mg tablets) and generic sildenafil. In England and Wales, over £11.1 million was spent on tadalafil once daily (tadalafil 2.5mg and 5mg tablets) over the course of a year (ePACT January to March 2016).

Switching to sildenafil on demand for ED could save over £8.9 million in England and Wales (based on 80% switch to sildenafil 8 tablets per month). **This equates to savings of £14,659 per 100,000 patients.**

As with all switches, consider individual patient circumstances. Tight switching criteria, assistance from practice nurses and support from local CCG prescribing teams will help GPs participate in realising the savings.

Summary

Tadalafil once daily (Cialis® 2.5mg and 5mg tablets) is licensed for ED in men who anticipate a frequent use of tadalafil (i.e. at least twice weekly).[3] This gives a potential advantage in that ED therapy could be taken without regard to timing of sexual activity. However, the available data do not suggest that taking tadalafil on a daily basis gives better results compared with on demand treatment in the general ED population.[8] This should be considered in the context of treatment costs, with tadalafil once daily costing between seven to 25 times more than treatment with generic sildenafil on demand.[41] Clinical evidence for the unlicensed use of PDE5 Inhibitors (including tadalafil once daily) in penile rehabilitation programmes is limited and conflicting.[11,33,34]

References

1. PrescQIPP DROP-List. Bulletin available at www.prescqipp.info
2. Summary of Product Characteristics. Viagra® film-coated tablets. Pfizer Ltd. Date of revision of the text October 2015. Accessed via www.emc.medicines.org.uk November 2015.
3. Summary of Product Characteristics. Cialis® film-coated tablets. Eli Lilly and Company. Date of revision of the text 14 August 2015. Accessed via www.emc.medicines.org.uk November 2015.
4. Summary of Product Characteristics. Levitra® film-coated tablets. Bayer Plc. Date of revision of the text 9 April 2014. Accessed via www.emc.medicines.org.uk November 2015.
5. Summary of Product Characteristics. Spedra® tablets. Menarini Farmaceutica Internazionale SRL. Date of revision of the text 18 September 2015. Accessed via www.emc.medicines.org.uk November 2015.
6. British Society for Sexual Medicine. Guidelines on the Management of Erectile Dysfunction, 2013. Available at http://www.bssm.org.uk/downloads/BSSM_ED_Management_Guidelines_2013.pdf Accessed November 2015.
7. Hatzimouratidis K, Eardley I et al. Guidelines on male sexual dysfunction: Erectile dysfunction and premature ejaculation. European Association of Urology, March 2015. http://uroweb.org/ Accessed November 2015.
8. Wrishko R, Sorsaburu R et al. Safety, Efficacy, and Pharmacokinetic Overview of Low-Dose Daily Administration of Tadalafil. The Journal of Sexual Medicine 2009;6:2039–2048.
9. Summary of Product Characteristics. Revatio® film-coated tablets. Pfizer Ltd. Date of revision of the text October 2015. Accessed via www.emc.medicines.org.uk November 2015.
10. Denby A. UKMi Q&A 128.2. What is the rationale and evidence for the use of phosphodiesterase-5 inhibitors for Erectile Dysfunction after radical prostatectomy? Date prepared August 2014. Accessed via https://www.evidence.nhs.uk August 2015
11. Fode M, Ohl D et al. Penile rehabilitation after radical prostatectomy: what the evidence really says. BJU International 2013;112:998-1008.
12. Kirby M, White I et al. Development of UK recommendations on treatment for post-surgical erectile dysfunction. The Internation Journal of Clinical Practice 2014; 68(5):590-608.
13. Health Service Circular HSC 1999/148: Treatment for Impotence. NHS Executive. Date issued 30 June 1999. http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4012086.pdf Accessed November 2015.
14. Health Service Circular HSC 1999/177: Treatment for Impotence, Patients with severe distress. NHS Executive. Date issued 6 August 1999. http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4012101.pdf Accessed November 2015.
15. National Institute for Health and Care Excellence (NICE). Type 1 diabetes in adults: diagnosis and management (NG17). 26 August 2015. https://www.nice.org.uk/guidance/ng17 Accessed November 2015.
16. National Institute for Health and Care Excellence (NICE). Type 2 diabetes in adults: management (NG28). 2 December 2015. https://www.nice.org.uk/guidance/ng28 Accessed March 2016.
17. National Institute for Health and Care Excellence (NICE). Myocardial infarction: cardiac rehabilitation and prevention of further MI (CG172). 13 November 2013. https://www.nice.org.uk/guidance/cg172 Accessed November 2015.
18. National Institute for Health and Care Excellence (NICE). Prostate cancer: diagnosis and management (CG175). 8 January 2014. https://www.nice.org.uk/guidance/cg175 Accessed November 2015.
19. Scottish Medicines Consortium tadalafil 2.5mg and 5mg film-coated tablets (Cialis®) (No: 554/09). Advice issued 8/5/09. Accessed via www.scottishmedicines.org.uk August 2015

20. National Collaborating Centre for Cancer (2014) Prostate cancer: diagnosis and treatment. NICE guideline (CG175) (Full guideline) January 2014. Cardiff UK. Accessed via http://www.nice.org.uk/guidance/cg175/evidence/prostate-cancer-full-guideline-191710765 on November 2015
21. Hackett G, Kell P et al. British Society for Sexual Medicine Guidelines on the Management of Erectile Dysfunction. The Journal of Sexual Medicine 2008;5:1841–1865.
22. National Institute for Health and Care Excellence (NICE). Lower urinary tract symptoms in men: management (CG97). 23 May 2010. https://www.nice.org.uk/guidance/cg97 Accessed November 2015.
23. National Institute for Health and Care Excellence (NICE). Tadalafil for the treatment of symptoms associated with benign prostatic hyperplasia (terminated appraisal) (TA273). 23 January 2013. https://www.nice.org.uk/guidance/ta273 Accessed November 2015.
24. Khera M, Goldstein I. Erectile dysfunction. Clinical Evidence 2011;06:1803 accessed via http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3217797/pdf/2011-1803.pdf August 2015.
25. National Institute for Health and Care Excellence (NICE). Erectile dysfunction: avanafil. Evidence summary: new medicine (ESNM45). 12 August 2014. https://www.nice.org.uk/guidance/esnm45 Accessed November 2015.
26. Moore R, Derry S et al. Indirect comparison of interventions using published randomised trials: systematic review of PDE-5 inhibitors for erectile dysfunction. BMC Urology 2005;5:18.
27. Berner M, Kriston L et al. Efficacy of PDE-5-inhibitors for erectile dysfunction. A comparative meta-analysis of fixed-dose regimen randomized controlled trials administering the International Index of Erectile Function in broad-spectrum populations. International Journal of Impotence Research 2006;18:229-235.
28. Tsertsvadze A, Fink H et al. Oral Phosphodiesterase-5 Inhibitors and Hormonal Treatments for Erectile Dysfunction: A Systematic Review and Meta-analysis. Annals of Internal Medicine 2009;151(9):650.
29. JinQiu Yuan, RenJie Zhang et al. Comparative Effectiveness and Safety of Oral Phosphodiesterase Type 5 Inhibitors for Erectile Dysfunction: A Systematic Review and Network Meta-analysis. European Urology 2013;63:902-912.
30. Seftel A. Re: Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: A systematic review and network meta-analysis. Journal of Urology 2013;190(4):1340.
31. Bang-Ping Jiann. Re: Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: A systematic review and network meta-analysis. European Urology 2014;65:e40.
32. London New Drugs Group Primary Care Briefing: Daily tadalafil. May 2009. Accessed via https://www.sps.nhs.uk/wp-content/uploads/2009/06/Daily20Tadalafil20Primary20Care20May2009.pdf on 2/12/15
33. Kadıoğlu A, Ortaç M et al. Tadalafil therapy for erectile dysfunction following prostatectomy. Therapeutic Advances in Urology 2015;7(3):146–151.
34. Gandaglia G, Suardi N et al. Penile rehabilitation after radical prostatectomy: does it work? Translational Andrology and Urology 2015;4(2):110-123.
35. Padma-Nathan H, McCullough A 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. International Journal of Impotence Research 2008;20:479–486.
36. Montorsi F, Brock G et al. Effects of Tadalafil Treatment on Erectile Function Recovery Following Bilateral Nerve-sparing Radical Prostatectomy:A Randomised Placebo-controlled Study (REACTT). European Urology 2014;65:587-596.
37. Montorsi F, Brock G et al. Effect of Nightly versus On-Demand Vardenafil on Recovery of Erectile Function in Men Following Bilateral Nerve-Sparing Radical Prostatectomy. European Urology 2008;54:924-931.

38. Miles C, Candy B et al. Interventions for sexual dysfunction following treatments for cancer. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD005540. DOI: 10.1002/14651858.CD005540.pub2. accessed via http://www.cochranelibrary.com December 2015
39. Montorsi F, Padma-Nathan H et al.Tadalafil in the treatment of erectile dysfunction following bilateral nerve sparing radical retropubic prostatectomy: A randomized, double-blind, placebo controlled trial. Journal of Urology 2004;172:1036–1041.
40. Smith II W, McCaslin I et al. PDE5 inhibitors: considerations for preference and long-term adherence. The International Journal of Clinical Practice 2013;67(8):768–780.
41. Drug Tariff May 2016. Accessed via http://www.nhsbsa.nhs.uk/PrescriptionServices/4940.aspx April 2016
42. MIMS Accessed via http://www.mims.co.uk April 2016
43. Summary of Product Characteristics. Sildenafil 50 mg film-coated tablets. Pfizer Ltd. Date of revision of the text December 2014. Accessed via www.emc.medicines.org.uk December 2015.

Additional PrescQIPP resources

 Briefing  Data pack

Available here: https://www.prescqipp.info/resources/category/297-tadalafil-once-daily-drop-list

Information compiled by Lindsay Wilson, PrescQIPP Programme, May 2016 and reviewed by Katie Smith, Senior Medicines Evidence Reviewer, June 2016.

Non-subscriber publication October 2016.

This document represents the view of PrescQIPP at the time of publication, which was arrived at after careful consideration of the referenced evidence, and in accordance with PrescQIPP's quality assurance framework.

The use and application of this guidance does not override the individual responsibility of health and social care professionals to make decisions appropriate to local need and the circumstances of individual patients (in consultation with the patient and/or guardian or carer).

Terms and conditions