EXPRESS SCRIPTS®

PRIOR AUTHORIZATION POLICY

POLICY: Erectile Dysfunction – Viagra® (sildenafil tablets – Pfizer; generics)

TAC APPROVAL DATE: 08/22/2018

OVERVIEW

Viagra is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5).[1] It enhances the effect of nitric oxide by inhibiting PDE5, which is responsible for degradation of cGMP in the corpus cavernosum of the penis. When sexual stimulation causes local release of nitric oxide, inhibition of PDE5 by Viagra causes increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum. Viagra is indicated for the treatment of erectile dysfunction (ED).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Viagra. All approvals are provided for the duration noted below.

Automation: When available, the ICD-9/ICD-10 codes for impotence of organic origin (ICD-9: 607.84) or male erectile dysfunction (ICD-10: N52.*) will be used for automation to allow approval of the requested medication. This automation is gender-selective and is not applicable for women; PDE5 inhibitor approval for use in women is always determined by prior authorization criteria.

Note: PDE5 inhibitors should not be administered, either regularly or intermittently, with concomitant nitrate therapy. Patients will be informed of the consequences should they initiate nitrate therapy while taking a PDE5 inhibitor.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Viagra is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Erectile Dysfunction (ED)**. Approve for 1 year.

   Viagra is indicated for the treatment of ED.[1]

Other Uses with Supportive Evidence

2. **Pulmonary Arterial Hypertension (PAH)**. Approve for 1 year.

   Revatio® (sildenafil tablets; generics) contains the same active ingredient as Viagra, sildenafil citrate, and is indicated for the treatment of PAH.[7] Viagra is available in 25 mg, 50 mg, and 100 mg tablets, and Revatio is available as 20 mg tablets. Viagra has been used for PAH based on case reports and placebo-controlled, double-blind studies.[8-19] Doses of Viagra that were used in these reports ranged from 25 mg twice daily (BID) to 100 mg five times daily. Patients will have usually been started on

Revatio 20 mg three times daily (TID). *Note:* PAH can be due to a variety of causes and is associated with many different conditions (e.g., Eisenmenger syndrome).

3. Raynaud's Phenomenon. Approve for 1 year if the patient meets one of the following criteria (A or B):

A) Patient has tried at least two of the following therapies for Raynaud disease: calcium channel blockers (e.g., amlodipine, felodipine, nifedipine), α-adrenergic blockers (e.g., prazosin), nitroglycerin, losartan, fluoxetine, or angiotensin converting enzyme (ACE) inhibitors; OR

B) Patient has tried one vasodilator (e.g., Flolan® [epoprostenol for injection], Edex® [alprostadil for injection], Tracleer® [bosentan tablets]).

Case reports indicate that Viagra 50 to 100 mg TID has been effective in patients with Raynaud phenomenon (usually with scleroderma) who have digital ischemia, gangrene, or ulcers.[20-23] In a double-blind, placebo-controlled, crossover study, 16 patients with symptomatic secondary Raynaud disease resistant to vasodilatory therapy received 50 mg of Viagra BID or placebo for 4 weeks.[24] While on Viagra, the mean frequency of Raynaud attacks was significantly lower, the cumulative attack duration was significantly shorter, and the mean Raynaud's Condition Score was significantly lower. Capillary blood flow velocity increased in every patient and the mean capillary flow velocity increased by > 400% in all patients after therapy with Viagra.

A consensus document published by the systemic sclerosis experts notes that for secondary Raynaud's phenomenon (i.e. due to systemic sclerosis) calcium channel blockers were the recommended first-line treatment in patients with mild (about 5 attacks/week) or more severe (about 25 attacks/week) attacks.[25] Consensus was not obtained for further treatment; however 35% of the surveyed experts recommended PDE5 inhibitors as second-line treatment for mild attacks and 45% would recommend it for more severe attacks. A meta-analysis of six trials assessing the efficacy of PDE5 inhibitors in secondary Raynaud's phenomenon showed moderate clinical benefit on Raynaud's Condition Score (RCS), frequency, and duration of attacks.[26] PDE5 inhibitors reduced the frequency of attacks by ~0.5/day compared with placebo, which is comparable reduction to calcium channel blockers (~0.6/day).

4. Benign Prostatic Hyperplasia (BPH). Approve for 1 year if the patient meets one of the following criteria (A or B):

A) Patient has tried an α_1-blocker (e.g., Cardura® XL [doxazosin extended-release tablets], terazosin tablets/capsules, tamsulosin capsules, alfuzosin extended-release tablets); OR

B) Patient has tried a 5α-reductase inhibitor (e.g., finasteride tablets, dutasteride capsules).

Note: For men with ED/BPH, use criterion 1 above.

In a 12-week, double-blind multicenter study with an 8-week open-label extension, 369 patients with lower urinary tract symptoms (LUTS) plus moderate ED were randomized to Viagra (50 mg nightly or 30 to 60 minutes before sexual activity for 2 weeks and then increased to 100 mg nightly for 10 weeks) or placebo.[27-28] Patients were not on 5α-reductase inhibitors or α_1-blockers during the study. After 12 weeks, the patients on Viagra had significant ($P < 0.0001$) improvements in erectile function (assessed with the International Index of Erectile Function [IIEF] questionnaire which was the primary outcome) and in LUTS measured by International Prostate Symptom Score (IPSS) change from baseline (one of the secondary outcomes), [-6.3 vs. -1.9, for Viagra and placebo, respectively; $P < 0.0001$]. The IPSS improvement observed with Viagra was comparable to results reported in α-blocker studies. There was no significant difference in urinary flow between the groups.

In another study (n = 36), Viagra statistically significantly increased IIEF and decreased IPSS, and IPSS-quality of life (QoL) at Day 30 in men with ED, inflammatory prostatitis, and LUTS (n = 22).[29] However, in men who had ED, LUTS, and asymptomatic inflammatory prostatitis (n = 14), Viagra lead to improvement in ED with no effect on LUTS symptoms.

A meta-analysis of several randomized controlled trials comparing PDE5 inhibitors vs. placebo or α_1-blockers, and PDE5 inhibitors in combination therapy with α_1-blockers was conducted.[30] A total of 12 studies were included in the analysis and the median follow-up for all trials was 12 weeks. The analysis of these trials showed that the use of PDE5 inhibitors alone was associated with a significant improvement of the IIEF score (+5.5; $P < 0.0001$) and IPSS (-2.8; $P < 0.0001$), but not in the maximum urinary flow rate (Q_{max}) compared with placebo. There were also statistically significant improvements in the IIEF score, IPSS score and Q_{max} for the combination of PDE5 inhibitors and α_1-blockers as compared with α_1-blockers alone.

The European Association of Urology (EAU) guidelines note that PDE5 inhibitors can be used in men with moderate-to-severe LUTS with or without ED.[31] The guidelines add that based on the results from a meta-analysis[30], younger men with lower body mass index and more severe LUTS benefit the most from PDE5 inhibitors.

5. **Prophylaxis After Radical Prostatectomy (Early Penile Rehabilitation).** Approve for 1 year in patients who meet the following criteria (A and B):
   A) Patient had radical prostatectomy within the previous 12 months; AND
   B) Viagra is prescribed by or in consultation with an urologist.

Data from studies in humans using the PDE5 inhibitors, Viagra or Levitra® (vardenafil tablets), are conflicting.[32] Several small studies with Viagra given on a daily basis have been favorable; however, a large trial with Levitra has suggested no benefit with once daily (QD) dosing. In the same trial, statistically significantly better outcome was noted with Levitra on-demand therapy compared with placebo.[33]

Viagra given on a daily basis has been used to improve the return of normal spontaneous erectile function, improve tissue oxygenation, and prevent penile fibrosis after nerve-sparing radical prostatectomy.[34-36]

In one study, 76 men with normal preoperative erectile function underwent bilateral nerve-sparing radical retropubic prostatectomy.[34] Four weeks after surgery, the patients were randomized in a double-blind fashion to Viagra 50 mg or 100 mg or to placebo given every night prior to sleep for 36 weeks. Erectile function was assessed 8 weeks after discontinuing drug therapy; no erectile dysfunction therapy was allowed when the double-blind therapy was stopped. Forty-eight weeks after surgery, 27% of patients on Viagra demonstrated return of spontaneous erectile function vs. 4% of patients on placebo ($P = 0.0156$).

In another report, 43 men who were sexually active before nerve-sparing radical prostatectomy (unilateral or bilateral) for prostate cancer were randomized to Viagra 25 mg/day (n = 23) at night starting on the day after indwelling catheter removal or to a control group (n = 18) who received no PDE5 inhibitors.[35] The IIEF-erectile function (EF) domain 5 (IIEF-EF) questionnaire was used to evaluate recovery of erectile function. IIEF-EF scores were > 16 (range 16 to 25) before surgery; possible scores range from 5 to 25 with severe ED 5 to 7, mild 17 to 21, and no ED 22 to 25. In the Viagra group, the mean IIEF-EF score decreased from 20.8 before surgery to 3.6, 3.8, 5.9, 9.6 and 14.1

at Weeks 6, 12, 24, 36 and 52, respectively with no additional on-demand Viagra. This was compared to the control group with mean IIEF-EF scores of 21.2, 2.4, 3.8, 5.3, 6.4, and 9.3 respectively. This was significantly different for IIEF-EF scores and time to recovery of erectile function between the two groups at weeks 36 and 52 ($P < 0.001$). In the Viagra group, 47% of patients attained and maintained a penile erection sufficient for vaginal intercourse at 1 year after surgery vs. 28% of patients in the control group. Also, the baseline potency was increased by using additional Viagra on demand (50 to 100 mg) to 86% overall potency with Viagra 25 mg/day vs. 66% in the control group.

In another small uncontrolled trial (n = 22) with mean follow-up of 6 months, early intracavernosal injections after bilateral nerve-sparing radical prostatectomy facilitated early sexual intercourse, patient satisfaction and potentially earlier return of natural erections.[36] Early combination therapy with Viagra 50 mg/day allowed a lower dose of intracavernous injections, minimizing penile discomfort.

In a single-institution, double-blind randomized study, nightly vs. on-demand efficacy of Viagra 50 mg was evaluated in patients post-radical prostatectomy.[40] Patients were treated for 12 months (6 tablets/month for on-demand dosing) with a 1-month washout period. When evaluated over all timepoints simultaneously, no significant effects of treatment group (either on-demand or nightly) were found on recovery of potency (assessed by IIEF-EF scores). In this study, the data do not show any significant benefit with nightly administration of Viagra compared with on-demand use.

The EAU guidelines on ED state that early use of pro-erectile drugs (therapeutic or prophylactic) following radical prostatectomy is important in achieving post-operative erectile function.[39] The guidelines note that PDE5 inhibitors are the first-line therapy in patients who have undergone nerve-sparing surgery, though in general post-radical prostatectomy patients are poor responders to PDE5 inhibitors. In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

6. **High-Altitude Pulmonary Edema (HAPE), Treatment or Prevention.** Approve for 1 year in patients who meet the following criteria (A and B):
   - **A)** Patient has HAPE or a history of HAPE; AND
   - **B)** Patient has tried one other pharmacologic therapy (i.e., nifedipine, Serevent® [salmeterol inhalation powder], dexamethasone, acetazolamide, Cialis® [tadalafil tablets]) for the treatment or prevention of HAPE.

Viagra 50 mg has been shown to significantly improve cardiac output and exercise capability and reduce systolic pulmonary artery pressure at rest and during exercise over placebo in healthy patients who ascended to a high altitude (5,400 m).[43] But, in another double-blind, randomized, placebo-controlled study (n = 62), daily administration of Viagra had no significant effect on pulmonary artery systolic pressure (PASP), which is a prerequisite for the development of HAPE, following a period of acclimatization at 3,650 meters.[44] Another PDE5 inhibitor, Cialis, was effective in a small double-blind study of 29 adult mountaineers with a history of HAPE.[45] Published guidelines for the prevention of HAPE recommend nifedipine as the preferred pharmacologic treatment option in patients who have a history of HAPE.[46] Other pharmacologic therapies mentioned in the guidelines for the prevention and/or treatment of HAPE include salmeterol, Cialis, Viagra, dexamethasone, or acetazolamide. For Viagra, published guidelines recommend a dose of 50 mg every 8 hours for the prevention of HAPE.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Viagra has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Annual revision	No criteria changes	07/15/2015
DEU revision	Changed automation section to include reference to ICD-10 code. The specific ICD-9 code was removed for diabetes and only the indication is listed.	10/12/2015
Selected revision	Changed approval duration back to 1 year for all indications.	12/02/2015
Selected revision	Removed automation which used ICD-9/ICD-10 codes (when available) for diabetes or claims history for diabetes medications (oral or insulin) as surrogate marker for erectile dysfunction. The new automation will use ICD-9 and/or ICD-10 codes for male erectile dysfunction when available. This new automation will be in effect 4/1/2016.	03/16/2016
Annual revision	Deleted "(Men or Women)" from Raynaud's phenomenon, pulmonary arterial hypertension, and high altitude pulmonary edema indications. Deleted all conditions listed under Conditions Not Recommended for Approval: women with antidepressant-associated sexual dysfunction, premature ejaculation, penile rehabilitation for erectile function of nonsurgical etiology, and female sexual arousal disorder.	08/03/2016
Annual revision	No criteria changes	08/09/2017
Annual revision	No criteria changes. Generic Viagra added.	08/22/2018

TAC – Therapeutic Assessment Committee; DEU – Drug Evaluation Unit; * For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx.