Erectile Dysfunction Prior Authorization with Quantity Limit Criteria Program Summary

Objective
The intent of the prior authorization (PA) program for Erectile Dysfunction (ED) is to ensure appropriate selection of patients for treatment according to product labeling and/or clinical guidelines. The PA program will approve PDE5 Inhibitors or prostaglandins for the treatment of ED when the patient's benefit plan covers ED agents, the patient is male, over eighteen years of age, and has a primary diagnosis of organic erectile dysfunction. Additionally, the patient cannot currently be prescribed another PDE5 inhibitor or a nitrate or nitric acid. In addition, Cialis/tadalafil 2.5 mg and 5 mg will be approved for patients with benign prostatic hyperplasia (BPH) who have already tried a generic alpha blocker or who have documented intolerance, FDA labeled contraindication, or hypersensitivity to available generic alpha blockers. Alpha blocker therapy must be discontinued prior to starting Cialis and the patient cannot be prescribed a nitrate or nitric acid. The program may approve PDE5 inhibitors for the accepted off-label uses of therapy of Raynaud's phenomenon in male and female patients and the preservation of erectile function following nerve-sparing radical retropubic prostatectomy in males.

Patients meeting the requirements of the PA criteria for treatment of ED with PDE5 inhibitors will be approved for a quantity of 30 tablets total for Cialis 2.5 mg and 5 mg or a quantity of 8 tablets for the other oral products. Patients meeting requirements for BPH will be approved for 30 tablets per month, for the requested agent Cialis 2.5 mg or 5 mg.

TARGET DRUGS
PDE5 Inhibitors:
Cialis® (tadalafil)
Levitra® (vardenafil)
Staxyn® (vardenafil)
Stendra® (avanafil)
Viagra® (sildenafil)

Prostaglandins:
Caverject® (alprostadil)
Caverject® Impulse (alprostadil)
Edex® (alprostadil)
Muse® (alprostadil)

QUANTITY LIMIT TARGET DRUGS - RECOMMENDED LIMITS (PDE5 Inhibitors Only)

Brand (generic)	GPI	Quantity per month
Cialis® (tadalafil)		
2.5 mg tablets	40304080000302	30
5 mg tablets	40304080000305	
10 mg tablets	40304080000310	8
20 mg tablets	40304080000320	

Levitra® (vardenafil)		
2.5 mg tablets	40304090100310	
5 mg tablets	40304090100320	
10 mg tablets	40304090100330	
20 mg tablets	40304090100340	
Staxyn® (vardenafil)		
10 mg orally disintegrating tablets	40304090107230	
Stendra® (avanafil)		
50 mg tablets	40304015000320	
100 mg tablets	40304015000330	
200 mg tablets	40304015000340	
Viagra® (sildenafil)		
25 mg tablets	40304070100310	
50 mg tablets	40304070100320	
100 mg tablets	40304070100330	

* Some groups cover less than or more than 8 tablets per month. Group specific policies will supersede this policy when applicable. Please refer to member's benefit plan. Only 1 oral agent will be covered per month.

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Prostaglandins will be approved when ALL of the following are met:

1. The patient's benefit plan covers agents for erectile dysfunction
   AND
2. The patient is at least 18 years of age and male
   AND
3. The patient has a diagnosis of erectile dysfunction that has persisted for at least six months and is secondary to an organic etiology, surgical procedure or injury (e.g. diabetes mellitus, vascular insufficiency, spinal cord injuries, prostatectomy)
   AND
4. The patient is not currently prescribed a nitrate or nitric oxide
   AND
5. The patient is not currently receiving another ED agent (oral, injectable or suppository)

Phosphodiesterase Type 5 Inhibitors will be approved when ONE of the following is met:

1. The patient's diagnosis is erectile dysfunction and ALL of the following:
   a. The patient's benefit plan covers agents for erectile dysfunction
      AND
   b. The patient is at least 18 years of age and male
      AND
   c. The patient has a diagnosis of erectile dysfunction that has persisted for at least six months and is secondary to an organic etiology, surgical procedure or injury (e.g. diabetes mellitus, vascular insufficiency, spinal cord injuries, prostatectomy)
      AND
   d. The patient is not currently prescribed a nitrate or nitric oxide
      AND
   e. The patient is not currently receiving another ED agent (oral, injectable or suppository)
      AND
   f. The quantity requested is less than or equal to the program quantity limit

   OR

2. The patient's diagnosis is benign prostatic hyperplasia (BPH) and ALL of the following:
    a. The requested agent is Cialis (tadalafil) 2.5 mg or 5 mg strength
    AND
    b. The patient is not currently prescribed a nitrate or nitric oxide
    AND
    c. The patient's medication history includes use of a generic alpha blocker OR the patient has documented intolerance, FDA labeled contraindication, or hypersensitivity to alpha blocker therapy
    AND
    d. The patient is not currently being treated with an alpha blocker OR the alpha blocker will be discontinued prior to starting Cialis (tadalafil)
    AND
    e. The quantity requested is within the program quantity limit

OR

3. The patient has a diagnosis of Raynaud's phenomenon AND ALL of the following:
    a. The patient is not currently prescribed a nitrate or nitric oxide
    AND
    b. The patient's medication history includes use of a dihydropyridine calcium channel blocker OR the patient has documented intolerance, FDA labeled contraindication, or hypersensitivity to calcium channel blocker therapy
    AND
    c. ONE of the following:
        i. The quantity requested is equal to or less than 60 tablets per month
        OR
        ii. The quantity requested is greater than 60 tablets per month and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

OR

4. The phosphodiesterase type 5 inhibitor has been prescribed for preservation of erectile function following a nerve-sparing radical retropubic prostatectomy AND ALL of the following:
    a. The patient is not currently prescribed a nitrate or nitric oxide
    AND
    b. The patient has been treated with the phosphodiesterase type 5 inhibitor for less than 12 months
    AND
    c. The quantity requested is equal to or less than 30 tablets per month

Note: Conditions (other than organic ED) for which sildenafil (Viagra®) may be covered include pulmonary hypertension (ICD-9 codes 416.0-416.9.) These requests will be reviewed on a case by case basis by Pharmacy Review.

Length of Approval:

Erectile dysfunction or Benign Prostatic Hyperplasia- 12 months

Raynaud's phenomenon – up to 60 tablets per month, or as approved by Clinical Review Pharmacist, for 12 months

Preservation of erectile function following a nerve-sparing radical retropubic prostatectomy – up to 30 tablets per month for a duration of up to 12 months

FDA APPROVED INDICATIONS AND DOSAGE[1-4,23, 26,27]

Agent	FDA Approved Indication	Dosage and Administration
Cialis (tadalafil)	Erectile Dysfunction (ED)	**ED; As needed:** Initially, 10 mg taken prior to anticipated sexual activity. Increase to 20 mg or decrease to 5 mg based upon efficacy and tolerability. Maximum recommended dosing frequency is once per day. Improves erectile function vs placebo up to 36 hours post dose. **ED; Once daily:** 2.5 mg taken once daily, without regard to timing of sexual activity. May increase to 5 mg based upon efficacy and tolerability.
	Benign Prostatic Hyperplasia (BPH)	**BPH:** 5 mg taken once daily; a starting dose of 2.5 mg daily is recommended if creatinine clearance is 30 to 50 mL/min. **BPH & ED:** 5 mg taken once daily, without regard to timing of sexual activity; a starting dose of 2.5 mg daily is recommended if creatinine clearance is 30 to 50 mL/min.
Levitra (vardenafil)	Erectile Dysfunction	For most patients, the starting dose is 10 mg, approximately 60 minutes before sexual activity. May be increased to a maximum dose of 20 mg or decreased to 5 mg based on efficacy and side effects. Maximum frequency is once per day.
Staxyn (vardenafil)	Erectile Dysfunction	The dose is 10 mg, approximately 60 minutes before sexual activity; The maximum dose is one tablet per day. Patients who require a lower or higher dose need to receive vardenafil film-coated tablets. Staxyn provides higher systemic exposure and is not interchangeable with vardenafil film-coated 10 mg tablets (Levitra).
Stendra (avanafil)	Erectile Dysfunction	For most patients, the recommended starting dose is 100 mg, approximately 30 minutes before sexual activity on an as needed basis; may be increased to maximum dose 200 mg or decreased to 50 mg based on efficacy and/or tolerability. Maximum frequency is once per day.
Viagra (sildenafil)	Erectile Dysfunction	For most patients, 50 mg as needed, approximately 1 hour before sexual activity. May be taken from 4 hours to 0.5 hour before sexual activity. Based on effectiveness and toleration, may be increased to a maximum dose of 100 mg or decreased to 25 mg. Maximum frequency is once per day.
Caverject (aprostadil injection)	Erectile Dysfunction	Dosing is carefully titrated for each patient under supervision by the physician. First injections must be done at the physician's office by medically trained personnel. Self-injection therapy can be started only after the patient is properly instructed and well trained. The dug is dosed between 1.25 mcg and 60 mcg, administered by intracavernosal injection. The

		maxiumum frequency of use is 3 doses weekly, with at least 24 hours between doses.
Caverject Impulse (alprostadil injection)	Erectile Dysfunction	Dosing is carefully titrated for each patient under supervision by the physician. First injections must be done at the physician's office by medically trained personnel. Self-injection therapy can be started only after the patient is properly instructed and well trained. The dug is dosed between 1.25 mcg and 60 mcg, administered by intracavernosal injection. The maxiumum frequency of use is 3 doses weekly, with at least 24 hours between doses.
Edex (alprostadil injection)	Erectile Dysfunction	Dosing is carefully titrated for each patient under supervision by the physician. First injections must be done at the physician's office by medically trained personnel. Self-injection therapy can be started only after the patient is properly instructed and well trained. The dug is dosed between 1.25 mcg and 60 mcg, administered by intracavernosal injection. The maxiumum frequency of use is 3 doses weekly, with at least 24 hours between doses.
Muse (alprostadil uretheral suppository)	Erectile Dysfunction	Patients should be individually titrated under the supervision of a physician to the lowest dose that is sufficient for sexual intercourse. The lower doses (125 mcg or 250 mcg) are recommended for initial dosing. The maximum frequency of use is 2 administrations per 24-hour period.

Limitations of Use:
If tadalafil is used with finasteride to initiate BPH treatment, such use is recommended for up to 26 weeks because the incremental benefit of tadalafil decreases from 4 weeks until 26 weeks, and the incremental benefit of tadalafil beyond 26 weeks is unknown.[1]

CLINICAL RATIONALE
Efficacy – Erectile Dysfunction (ED)
American Urological Association (AUA) guidelines state that oral phosphodiesterase type 5 (PDE5) inhibitors, unless contraindicated, should be offered as a first-line therapy for ED. Sildenafil, tadalafil, vardenafil, and avanafil are potent, reversible, competitive inhibitors of PDE5. At this time, there is insufficient evidence to support the superiority of one agent over the others. Currently, there are not sufficient data to counsel patients on the likelihood of success with a different PDE5 inhibitor if they failed an "adequate" trial with one drug. Once an adequate trial has been completed with one drug and all modifiable risk factors have been addressed, the patient may be treated with a different PDE5 inhibitor or proceed with other, more invasive therapies for ED.[5,23] Other options include intra-urethral alprostadil, intracavernous vasoactive drug injection, vacuum constriction devices, and penile prosthesis implantation.[4]

Sexual behavior studies indicate that commonly prescribed PDE5 inhibitor quantities range from 3 to 6 tablets per patient per month.[6]

Efficacy – Benign Prostatic Hyperplasia (BPH)
The efficacy and safety of tadalafil for once daily use for the treatment of the signs and symptoms of BPH was evaluated in 3 randomized, multinational, double-blinded, placebo-controlled, parallel-design, efficacy and safety studies of 12 weeks duration. Two of these studies were in men with BPH and one study was specific to men with both ED and BPH. The

primary efficacy endpoint in the two studies that evaluated the effect of tadalafil for the signs and symptoms of BPH was the International Prostate Symptom Score (IPSS), a four week recall questionnaire that was administered at the beginning and end of a placebo run-in period and subsequently at follow-up visits after randomization. The IPSS assesses the severity of irritative (frequency, urgency, nocturia) and obstructive symptoms (incomplete emptying, stopping and starting, weak stream, and pushing or straining), with scores ranging from 0 to 35; higher numeric scores representing greater severity. Maximum urinary flow rate (Qmax), an objective measure of urine flow, was assessed as a secondary efficacy endpoint in Study J and a safety endpoint in Study K.[1]

The results for BPH patients with moderate to severe symptoms and a mean age of 63.2 years (range 44 to 87) who received either tadalafil 5 mg for once daily use or placebo (N=748) in Studies J and K showed statistically significant improvement in the total IPSS compared to placebo. Mean total IPSS showed a decrease starting at the first scheduled observation (4 weeks) in Study K and remained decreased through 12 weeks. In Study J, the effect of tadalafil 5 mg once daily on maximum urinary flow rate (Qmax) was evaluated as a secondary efficacy endpoint. Mean Qmax increased from baseline in both the treatment and placebo groups (tadalafil 5 mg: 1.6 mL/sec, placebo: 1.2 mL/sec); however, these changes were not significantly different between groups. In Study K, the effect of tadalafil 5 mg once daily on Qmax was evaluated as a safety endpoint. Mean Qmax increased from baseline in both the treatment and placebo groups (tadalafil 5 mg: 1.6 mL/sec, placebo: 1.1 mL/sec); however, these changes were not significantly different between groups.[1]

The efficacy and safety of tadalafil for once daily use for the treatment of ED, and the signs and symptoms of BPH, in patients with both conditions was evaluated in one placebo-controlled, multinational, double-blind, parallel-arm study which randomized 606 patients to receive either tadalafil 2.5 mg, 5 mg, for once daily use or placebo. ED severity ranged from mild to severe and BPH severity ranged from moderate to severe. The full study population had a mean age of 63 years (range 45 to 83). Patients with multiple co-morbid conditions such as diabetes mellitus, hypertension, and other cardiovascular disease were included. In this study, the co-primary endpoints were total IPSS and the Erectile Function (EF) domain score of the International Index of Erectile Function (IIEF). Tadalafil 2.5 mg (N = 198) and 5 mg (N = 208) significantly improved IIEF-EF domain scores (both $P < 0.001$) vs. placebo (N = 200) at end point. For IPSS, improvements were significant with tadalafil 5 mg ($P < 0.001$), but not 2.5 mg, for observations from 2 weeks through end point.[22] In this study, the effect of tadalafil 5 mg once daily on Qmax was evaluated as a safety endpoint. Mean Qmax increased from baseline in both the treatment and placebo groups (tadalafil 5 mg: 1.6 mL/sec, placebo: 1.2 mL/sec); however, these changes were not significantly different between groups.[1]

The exact mechanism of action by which tadalafil reduces LUTS associated with BPH has not been established. One proposed mechanism of action involves cyclic guanosine monophosphate (cGMP) mediated smooth muscle relaxation in the prostatic stroma and capsule.[20] Similarly, the beneficial effect of alpha blockers is due to relaxation of smooth muscles in the bladder neck and prostate. Both tadalafil and alpha blockers demonstrate efficacy within days to weeks. This contrasts with 5-alpha reductase inhibitors which shrink the prostate and require a longer duration of use before benefit is seen.[21]

Raynaud's Phenomenon

The standard drug therapy for patients who have Raynaud's phenomenon is a calcium channel blocker. The dihydropyridines are potent vasodilators and are efficacious in the treatment of Raynaud's phenomenon. Although nifedipine has been studied most extensively, the newer dihydropyridines, including felodipine, amlodipine, and isradipine, seem to be equally effective.[7]

The available evidence indicates that sildenafil is associated with improved microcirculation, symptomatic relief, and ulcer healing in patients with Raynaud's phenomenon, when treatment with vasodilators such as calcium channel blockers has failed.[7-9] More limited data suggest similar effects with tadalafil and vardenafil.[8,10]

In a double-blind, placebo-controlled, fixed-dose crossover study, the effect of sildenafil on symptoms of capillary perfusion was investigated in 16 patients with symptomatic secondary Raynaud's phenomenon that was resistant to vasodilator therapy (failure of two vasodilatory agents).[9] After four weeks of therapy (sildenafil 50 mg twice daily), sildenafil patients demonstrated reduction in the frequency of attacks (35 vs 52, p=0.0064) and significantly shortened the duration of attacks (581 minutes vs 1046 minutes, p=0.0386). Capillary blood flow velocity increased in each patient. Six of the patients with chronic digital ulcerations experienced visible healing of the ulcers during treatment. In two patients, ulcerations completely disappeared. Ulcerations reappeared or progressed again after treatment was discontinued.[9]

Caglayan, et al,[10] conducted an open-label pilot study in 40 patients with Raynaud's phenomenon, 33 (82%) of whom had secondary and 7 (18%) of whom had primary disease. Digital blood flow was measured by laser-Doppler flowmetry at room temperature and during the cold-exposure test before medical treatment, 1 hour after the initial intake, and after 2 weeks of continuous treatment (10 mg twice a day) with vardenafil. Clinical symptoms were recorded by a patient questionnaire and summarized as the Raynaud condition score. Laser-Doppler flowmetry revealed that vardenafil improved digital blood flow in 28 (70%) patients, whereas 12 (30%) did not respond. In individuals responding, digital blood flow significantly increased by a mean ± SEM of 21.0% ± 4.9% and 30.0% ± 5.7% at 1 hour and 2 weeks of treatment at room temperature, respectively, and by 18.8% ± 4.4% and 35.1% ± 7.5% at 1 hour and 2 weeks during the cold-exposure test, respectively (P <.01 for all). Consistently, clinical symptoms improved in 27 (68%) of the 40 patients, and the Raynaud condition score declined from a mean ± SEM of 5.05±0.38 to 3.54±0.31 (P <.001).[10]

Roustit et al[24] conducted a systematic review of controlled trials which assessed the efficacy of PDE5 inhibitors in secondary Raynaud's phenomenon. Their sources included Medline, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials. Only double-blind, randomized controlled trials (RCTs) were included. Studies were selected independently by two authors using predefined data fields, including study quality indicators. Six RCTs were included (one with sildenafil, one with modified-release sildenafil, three with tadalafil and one with vardenafil). PDE5 inhibitors significantly decreased mean Raynaud's Condition Score by −0.46 (−0.74 to −0.17) (p=0.002), the daily frequency of ischemic attacks by −0.49 (−0.71 to −0.28) (p<0.0001), and daily duration of Raynaud's phenomenon attacks by −14.62 (−20.25 to −9.00) min (p<0.0001). The authors concluded that PDE5 inhibitors appear to have significant but moderate efficacy in secondary Raynaud's phenomenon and that a further large RCT is needed. [24]

Preservation of Erectile Function following Prostatectomy

Available evidence regarding prophylactic treatment with PDE5 inhibitors indicates that early treatment with regularly scheduled dosing may preserve smooth muscle content and improve erectile function in men undergoing nerve-sparing radical retropubic prostatectomy (RRP).[11-15] The loss of intracorporeal smooth muscle (SM) and an increase in intracorporeal fibrosis have been demonstrated in vasculogenic impotence and implicated in permanent post-RRP erectile dysfunction.

Schwartz et al.[11] assessed the effect of sildenafil on intracorporeal SM content after RRP. A total of 40 potent volunteers with prostate cancer underwent RRP and were divided into 2 treatment groups, namely 1-50 mg sildenafil and 2-100 mg sildenafil every other night for 6 months beginning the day of catheter removal. Percutaneous biopsy was performed using general anesthesia prior to incision for RRP and again using local anesthesia 6 months later. Volunteers were excluded prior to the second biopsy if they discontinued sildenafil. Biopsies were stained for SM and connective tissue, and analyzed by computer in at least 15 different fields. A total of 11 patients in group 1 and 10 in group 2 underwent the second biopsy. In group 1 there was no statistically significant change in mean SM content preoperatively to postoperatively (51.52% and 52.67%, respectively). In group 2 there was a statistically significant increase in mean SM content 6 months after RRP (42.82% vs 56.85%, $p < 0.05$). The authors concluded that early use of sildenafil after RRP may preserve intracorporeal SM content. At higher doses post-RRP sildenafil may increase SM content. The effect on the return of potency is not known but maintaining the pro-erectile ultrastructure is integral to rehabilitating post-RRP erectile function.

Mulhall et al.[12] challenged men with functional preoperative erections who underwent radical prostatectomy (RP) with oral sildenafil early postoperatively. Nonresponders were switched to intracavernosal injection therapy (ICI). Patients were instructed to inject three times a week. Patients had to present within 6 months post RP, complete the International Index of Erectile Function (IIEF) questionnaire on at least three separate occasions after surgery, and be followed for at least 18 months. Data from men who were committed to rehabilitation were compared with those of men who did not follow the protocol but continued to be followed serially following RP. There were 58 patients in the rehabilitation (R) group and 74 in the nonrehabilitation (NR) group. No differences existed in mean patient age, comorbidity profile, intraoperative nerve sparing status, or postoperative erectile hemodynamics between the two groups. At 18 months post RP, there were statistically significant differences between the two groups in the percentage of patients who were capable of having medication-unassisted intercourse (R=52% vs. NR=19%, $P<0.001$). Those in the rehabilitation group also had improved mean erectile rigidity, mean IIEF erectile function (EF) domain scores, and increased percentage of patients responding to sildenafil or ICI. The data generated from this nonrandomized study indicate that a pharmacologic penile rehabilitation protocol results in higher rates of spontaneous functional erections and erectogenic drug response after RP.

Padma-Nathan et al.[14] studied sildenafil in a primary prevention modality using nightly administration after a bilateral nerve-sparing prostatectomy. In this novel approach, it effected a sevenfold improvement in return of spontaneous, normal erectile function 2 months after drug discontinuation.[14] Additional studies with nightly vardenafil for up to 9 months have shown improved recovery of erectile function with PDE5 therapy.[16-19]

A 2013 study assessed the effects of avanafil in men with mild to severe ED for ≥ 6 months following bilateral nerve-sparing radical prostatectomy.[34] This was a double-blind, placebo controlled, parallel group, phase 3 study in males age 18 to 70 years with a history of ED of 6 months or more after bilateral nerve sparing radical prostatectomy. [34]
Patients were randomized to 100 or 200 mg avanafil or placebo (taken 30 minutes before sexual activity) for 12 weeks. Primary end points included successful vaginal insertion (SEP [2]) successful intercourse (SEP [3]) and change in score on the erectile function domain of the IIEF-EF questionnaire.[25]

A total of 298 patients were randomized and 84.6% completed the study. At baseline 16.1% were age 65 years or older and 71.5% had severe ED (mean overall IIEF-EF domain score 9.2). After 12 weeks there were significantly greater increases in SEP2 and SEP3 and change in mean IIEF –EF domain score with 100 and 200 mg avanafil vs placebo ($p < 0.01$).

Following dosing with avanafil 36.4% (28 of 77) of sexual attempts (SEP3) at 15 minutes or less were successful vs 4.5% (2 of 44) for placebo (p <0.01). Avanafil was generally well tolerated.[25]

Safety

The side effect profiles of the PDE5 inhibitors are similar. These medications have side effects due to peripheral vasodilation such as facial flushing, nasal congestion, headache, and dyspepsia. When considering PDE5 inhibitors for the management of ED, physicians should be aware that even healthy volunteers may experience mild transient systemic vasodilation; this effect may be aggravated by other medications (e.g., alpha-blockers). PDE5 inhibitors potentiate the hypotensive effects of nitrates and nitrites, and therefore their concomitant use is contraindicated.[5] Due to an increased risk of hypotension with the concomitant use of PDE5 inhibitors and guanylate cyclase stimulators, such as riociguat, use together is contraindicated.[1-4,21,23]

Alprostadil is contraindicated in patients with sickle cell anemia or trait, multiple myeloma or leukemia.[1-3] Use of alprostadil injections is contraindicated in patients with penile implants, the use of urethral suppositories has not been evaluated in patients with implants.[3]

The safety and efficacy of erectile dysfunction agent combinations has not been extensively studied.[1-3,6,7] Small studies evaluating alprostadil combined with a PDE5 agent report response rates of ninety-two to one hundred percent in patients who did not respond to oral sildenafil alone.[5] Double blind randomized controlled clinical trials are needed to establish benefits, optimal dosage, and possible adverse effects before combination therapy can be recommended.

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