Cigna Drug and Biologic Coverage Policy

Subject **Oral Phosphodiesterase-5 (PDE5) Inhibitors**

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Table of Contents

Related Coverage Resources

Male Sexual Dysfunction Treatment: Non-pharmacologic
Pulmonary Hypertension (PH) Therapy
Quantity Limitations

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

This coverage policy addresses the use of oral phosphodiesterase-5 (PDE5) inhibitors for erectile dysfunction, benign prostatic hyperplasia, and other covered off-label uses. The use of PDE5 inhibitors (Adcirca, Revatio) for pulmonary hypertension is addressed in a separate coverage policy. Please refer to the related coverage policy link above.

For Erectile Dysfunction Uses:

Note: Erectile dysfunction therapy is specifically excluded under many benefit plans [both Employer Groups and Individual and Family Plans]. Please refer to the applicable benefit plan document to determine benefit availability and the terms and conditions of coverage (for example, quantities covered).

If coverage is available for erectile dysfunction, then Cigna covers oral phosphodiesterase-5 (PDE5) inhibitors as medically necessary for the following criteria:

For Employer Group Benefit Plans:

Product	Criteria for Use
Sildenafil* **Tadalafil [5mg, 10mg and 20mg]***	**Treatment of adult male erectile dysfunction (age 19 and older)**

Tadalafil [daily 2.5 mg or 5 mg]** **Vardenafil***	*where covered, a maximum quantity limitation up to 8 tablets per 30 days is allowed ** where covered, a maximum quantity limitation of 30 tablets per 30 days is allowed
Cialis® (brand name)* [5mg, 10mg, 20mg] **Cialis® (brand name)** [daily 2.5 mg or 5 mg]** **Levitra® (brand name)* or Staxyn™ (brand name)*** **Stendra™ (avanafil)*** **Viagra® (brand name)***	**Treatment of adult male erectile dysfunction (age 19 and older) when the following criteria are met:** • Documented failure, contraindication per FDA label, or intolerance to sildenafil **OR** tadalafil **OR** vardenafil *where covered, a maximum quantity limitation up to 8 tablets per 30 days is allowed ** where covered, a maximum quantity limitation of 30 tablets per 30 days is allowed

<u>For Benign Prostatic Hyperplasia (BPH) Use:</u>

Tadalafil or Cialis® [2.5* mg or 5 mg] is considered medically necessary for the treatment of benign prostatic hyperplasia (BPH) when the following criteria are met:

- **For Employer Group Benefit Plans**:
  - For tadalafil
    - Documented failure / inadequate response, contraindication per FDA label, or intolerance to one of the following: alfuzosin, doxazosin, finasteride, tamsulosin, dutasteride, or Jalyn®
  - For Cialis® (brand name) All of the following:
    - Documented failure / inadequate response, contraindication per FDA label, or intolerance to one of the following: alfuzosin, doxazosin, finasteride, tamsulosin, dutasteride, or Jalyn®
    - Documented intolerance to tadalafil

- **For Individual and Family Plan (IFP)**: Documented failure, contraindication per FDA label, or intolerance to **BOTH** of the following:
  - One of the following Alpha-blockers: alfuzosin, doxazosin, or tamsulosin
  - One of the following 5-Alpha Reductase Inhibitors: finasteride, dutasteride

** Cialis 2.5 mg once daily will be covered for BPH when meeting criteria above AND when individual is not a candidate for Cialis 5 mg once daily (for example: creatinine clearance of 30-50 ml/min; concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir).*

Quantity limitation of 30 tablets per 30 days.

<u>Off-label Use(s):</u>

Oral Phosphodiesterase-5 Inhibitors (sildenafil and tadalafil) are considered medically necessary for the treatment of Raynaud's disease when the following criteria are met:

- **For Employer Group Benefit Plans**:
  - For sildenafil or tadalafil
    - Documented failure, contraindication per FDA label, or intolerance to a calcium channel blocker (For example, nifedipine, diltiazem)
  - For Cialis® (brand name) All of the following:
    - Documented failure, contraindication per FDA label, or intolerance to a calcium channel blocker (For example, nifedipine, diltiazem)

        - Documented intolerance to tadalafil
        - Documented failure, contraindication per FDA label, or intolerance to sildenafil
    - For Viagra® (brand name) All of the following:
        - Documented failure, contraindication per FDA label, or intolerance to a calcium channel blocker (For example, nifedipine, diltiazem)
        - Documented intolerance to sildenafil
        - Documented failure, contraindication per FDA label, or intolerance to tadalafil

- **For Individual and Family Plan (IFP)**:
    - For Cialis (brand name), sildenafil, tadalafil, and Viagra
        - Documented failure, contraindication per FDA label, or intolerance to a calcium channel blocker (For example, nifedipine, diltiazem)

Initial authorization is up to 12 months unless otherwise stated.

Oral PDE5 Inhibitors are considered medically necessary for continued use when the initial criteria are met.

Reauthorization is up to 12 months.

Oral Phosphodiesterase-5 Inhibitors are considered experimental, investigational or unproven for ANY other use including the following (this list may not be all-inclusive):

- premature ejaculation (PE)
- sexual dysfunction in females
- Duchenne muscular dystrophy
- cystic fibrosis lung disease
- lower uretic stones
- left ventricular function in resistant hypertension
- continence recovery “re-enervation” status post radical prostatectomy
- esophageal achalasia
- lower urinary tract symptoms

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to Oral Phosphodiesterase-5 (PDE5) Inhibitors therapy.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage

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FDA Approved Indication

Product	Indication
avanafil (Stendra™) **sildenafil (Viagra®)** **tadalafil (Cialis®)** **vardenafil (Levitra® or Staxyn™)**	Indicated for the treatment of erectile dysfunction.
tadalafil (Cialis®)	Indicated for the treatment of ED and the signs and symptoms of BPH (ED/BPH).
tadalafil (Cialis®)	Indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). Limitation of Use: If Cialis is used with finasteride to initiate BPH treatment, such use is recommended for up to 26 weeks because the incremental benefit of Cialis decreases from 4 weeks until 26 weeks, and the incremental benefit of Cialis beyond 26 weeks is unknown.

FDA Recommended Dosing

Product	Dosing
avanafil (Stendra™)	The recommended starting dose is 100 mg. Stendra should be taken orally as needed as early as approximately 15 minutes before sexual activity. Based on individual efficacy and tolerability, the dose may be increased to 200 mg taken as early as approximately 15 minutes before sexual activity, or decreased to 50 mg taken approximately 30 minutes before sexual activity. The lowest dose that provides benefit should be used. The maximum recommended dosing frequency is once per day. Sexual stimulation is required for a response to treatment.
sildenafil (Viagra®)	For most patients, the recommended dose is 50 mg taken, as needed, approximately 1 hour before sexual activity. However, Viagra may be taken anywhere from 30 minutes to 4 hours before sexual activity. The maximum recommended dosing frequency is once per day. Based on effectiveness and toleration, the dose may be increased to a maximum recommended dose of 100 mg or decreased to 25 mg.
tadalafil (Cialis®)	Do not split Cialis tablets; entire dose should be taken. <u>Cialis for Use as Needed for Erectile Dysfunction</u> The recommended starting dose of Cialis for use as needed in most patients is 10 mg, taken prior to anticipated sexual activity. The dose may be increased to 20 mg or decreased to 5 mg, based on individual efficacy and tolerability. The maximum recommended dosing frequency is once per day in most patients. <u>Cialis for Once Daily Use for Erectile Dysfunction</u> The recommended starting dose of Cialis for once daily use is 2.5 mg, taken at approximately the same time every day, without regard to timing of sexual activity. The Cialis dose for once daily use may be increased to 5 mg, based on individual efficacy and tolerability. <u>Cialis for Once Daily Use for Benign Prostatic Hyperplasia</u> The recommended dose of Cialis for once daily use is 5 mg, taken at approximately the same time every day. Note: When therapy for BPH is initiated with Cialis and finasteride, the recommended dose of Cialis for once daily use is 5 mg, taken at approximately the same time every day for up to 26 weeks. <u>Cialis for Once Daily Use for Erectile Dysfunction and Benign Prostatic Hyperplasia</u> The recommended dose of Cialis for once daily use is 5 mg, taken at approximately the same time every day, without regard to timing of sexual activity. There is no evidence establishing the safety and efficacy of concomitant use of Cialis for daily use and Cialis for use as needed.
vardenafil (Levitra®)	For most patients, the recommended starting dose of Levitra is 10 mg, taken orally, as needed, approximately 60 minutes before sexual activity. The dose may be increased to a maximum recommended dose of 20 mg or decreased to 5 mg based on efficacy and side effects. The maximum recommended dosing frequency is once per day. Sexual stimulation is required for a response to treatment.
vardenafil (Staxyn™)	Staxyn is available in 10 mg orally disintegrating tablets. Staxyn is not interchangeable with vardenafil 10 mg film-coated tablets (Levitra). Staxyn provides higher systemic exposure compared to vardenafil 10 mg film-coated tablets (Levitra).

	Staxyn should be taken orally, as needed, approximately 60 minutes before sexual activity. The maximum dosing frequency is one Staxyn tablet per day. Sexual stimulation is required for a response to treatment. Staxyn should be placed on the tongue where it will disintegrate. Those patients who require a lower or higher dose of vardenafil need to be prescribed vardenafil film-coated tablets.

Drug Availability

Product	Dosing
Cialis	Cialis is supplied as four strengths of film-coated, almond-shaped tablets (not scored) available in different sizes and different shades of yellow and supplied in the following package sizes: 2.5 mg tablets debossed with “C 2 1/2”; 5-mg tablets debossed with “C 5”; 10-mg tablets debossed with “C 10”; and 20-mg tablets debossed with “C 20”.
Levitra	Levitra is formulated as orange, film-coated round tablets with debossed “BAYER” cross on one side and “2.5”, “5”, “10”, and “20” on the other side equivalent to 2.5 mg, 5 mg, 10 mg, and 20 mg of vardenafil, respectively.
Staxyn	Staxyn (vardenafil HCl) are white, round orally disintegrating tablets with no debossing. Staxyn orally disintegrating tablets are packaged into foil blisterpacks and supplied as a 4 tablet unit. One blister card contains (4) 10 mg tablets.
Stendra	Stendra is supplied as oval, pale yellow tablets containing 50 mg, 100 mg, or 200 mg avanafil debossed with dosage strength.
Viagra	Viagra is supplied as blue, film-coated, rounded-diamond-shaped tablets containing sildenafil citrate equivalent to the nominally indicated amount of sildenafil of 25mg, 50mg, or 100mg in bottles of 30 or 100.

General Background

Pharmacology
The most abundant phosphodiesterase in the corpus cavernosum is phosphodiesterase-5 (PDE5). Therefore, the inhibition of PDE5 enhances erectile function by increasing the amount of cGMP in the corpus cavernosum. Sexual stimulation is required to initiate the local release of nitric oxide; therefore, PDE5I’s have no effect in the absence of sexual stimulation. (McEvoy, 2017)

Guidelines

- Benign Prostatic Hyperplasia (BPH)
  The American Urological Association (AUA) guideline for the Management of Benign Prostatic Hyperplasia (BPH) states for patients with mild symptoms of LUTS secondary to BPH (AUA-SI score <8) and patients with moderate or severe symptoms (AUA-SI score ≥8) who are not bothered by their LUTS should be managed using a strategy of watchful waiting (active surveillance). The guideline recommend alpha blockers, 5-alpha reductase inhibitors, anticholinergics, and combination therapy (alpha blocker and 5-alpha reductase inhibitor) for the treatment of LUTS secondary to BPH.
  The guidelines state that alpha blockers are the mainstay of LUTS/BPH therapy. The guidelines note no differences in efficacy among doxazosin, tamsulosin, terazosin and alfuzosin in the management of BPH and that there is no evidence to suggest that the clinical efficacy of 5-alpha reductase inhibitors differs when used for the appropriate indication.
  The guideline currently does not have a recommendation for the place in therapy for PDE5 inhibitors. (McVary, 2014)

- Erectile Dysfunction
  The American Urological Association guidelines for Erectile Dysfunction state that the management of ED begins with the identification of organic and psychosexual dysfunctions and that both should be treated or their care triaged. The guidelines also suggest that oral PDE5s, unless contraindicated, should be offered as a first-line of therapy of erectile dysfunction. However, PDE5s are contraindicated in patients who are taking organic nitrates. (AUA, 2018)

- Lower Urinary Tract Symptoms (LUTS) - Male
  The European Association of Urology guideline for Lower Urinary Tract Symptoms (LUTS) in males states that LUTS now constitute the main focus, rather than the former emphasis on Benign Prostatic Hyperplasia (BPH). The management of mild/moderate LUTS begins with watchful waiting and behavioral/dietary modifications. The list of recommended pharmacologic treatment choices includes alpha blockers, 5-alpha reductase inhibitors, anticholinergics, beta-3 agonists, combination therapy (alpha blocker and 5-Alpha Reductase Inhibitor or alpha blocker and anticholinergics). The guideline suggests that PDE5 inhibitors are effective for reducing moderate-to-severe LUTS symptoms. Alpha blockers are considered first-line drug treatment of male LUTS because of their rapid onset of action, good efficacy, and favorable adverse effects profile. The guidelines note that all alpha-adrenergic blocking agents have similar efficacy at appropriate doses, and that available evidence indicates that dutasteride and finasteride are equally effective in the treatment of LUTS. Tadalafil 5mg daily has only been studied in male LUTS, secondary to Benign Prostatic Hyperplasia (BPH), with or without erectile dysfunction; however, long-term experience with tadalafil is limited to a single trial in the BPH patient population where tadalafil is already indicated. Further limitations include only a one year follow-up, limited information on reduction of prostate size, and no data on disease progression. (EAU, 2017)

  National Institute for Health and Care Excellence (NICE) Guideline for LUTS in men advises against the use of phosphodiesterase-5 inhibitors solely for the purpose of treating lower urinary tract symptoms in men. NICE states that more evidence is needed to enable a recommendation to be made on the use of phosphodiesterase-5 inhibitors in all men with LUTS, including those without erectile dysfunction. (NICE, 2015)

Clinical Efficacy for Other Covered Uses:
Raynaud's Phenomenon
Erectile Dysfunction agents have been studied for use in Raynaud's disease (RD) and Raynaud's phenomenon (RP). Raynaud's manifests as recurrent vasospasm of the fingers and toes and usually occurs in response to exposure to emotional stress or cold temperatures. Current treatment includes patient education, discontinuing vasoconstricting agents such as nicotine and caffeine, warming the affected local body part, and use of medications. Medications include: calcium channel blockers, angiotensin receptor antagonists, intravenous prostaglandins, selective serotonin uptake inhibitors, and anti-platelet agents. (Thompson, 2001).

A 2013 meta-analysis of double-blind, randomized controlled trials evaluated the utility of PDE5 inhibitors in secondary Raynaud's phenomenon (RP) (Roustit, 2013). The meta-analysis reviewed six trials (one sildenafil [dosed 50 mg twice daily], one modified-release sildenafil [dosed 100 mg once daily for 3 days, then 200 mg once a day for 25 days], one vardenafil [dosed 10 mg twice daily] and three tadalafil [one trial dosed 20 mg once daily; 2 trials dosed as add-on therapy 20 mg on alternate days]; n=244). Eligibility criteria included parallel or cross-over double-blind, randomized controlled trials which studied the efficacy of PDE5 inhibitors on secondary RP. Outcomes were the Raynaud's Condition Score (RCS), daily frequency of RP attacks, and daily duration of RP attacks. PDE5 inhibitors demonstrated to significantly improve RCS and frequency and duration in RP attacks compared with placebo in secondary RP. PDE5 inhibitors were also shown to reduce the frequency of RP attacks by approximately 0.5/day compared with placebo, which is a comparable reduction to that found by another meta-analysis assessing the efficacy of calcium channel blockers in Systemic Sclerosis related RP (approximately 0.6/day) (Thompson, 2001).

Experimental Investigational, Unproven Uses
There is insufficient evidence in the peer-reviewed published scientific literature to support safety and efficacy of PDE5 Inhibitors in premature ejaculation (PE) (Montague, 2004), sexual dysfunction in females (Goa, 2016), Duchenne muscular dystrophy (Nelson, 2014; Victor, 2017), cystic fibrosis lung disease (Taylor-Cousar, 2015), lower uretic stones (Kumar, 2015), left ventricular dysfunction in resistant hypertension (Santos, 2014), continence recovery "re-enervation" status post radical prostatectomy (Gacci, 2010), esophageal achalasia (Eherer, 2002), and lower urinary tract symptoms (NICE, 2015)

Coding/Billing Information

Note: Oral phosphodiesterase-5 (PDE5) inhibitors are typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions, therefore, this section is not in use.

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