



EXPRESS SCRIPTS®

PRIOR AUTHORIZATION POLICY

POLICY: Erectile Dysfunction

- Levitra® (vardenafil tablets – Bayer/GlaxoSmithKline)
- Staxyn™ (vardenafil orally disintegrating tablet – Bayer/GlaxoSmithKline)

TAC APPROVAL DATE: 08/22/2018

OVERVIEW

Levitra and Staxyn are selective inhibitors of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). They are indicated for the treatment of erectile dysfunction (ED).¹ Levitra is available as a 2.5 mg, 5 mg, 10 mg, and 20 mg film-coated tablet and Staxyn is available as a 10 mg orally disintegrating tablet (ODT).¹⁻² Because the ODT provides a higher systemic exposure than the film-coated tablet, the 10 mg ODT and film-coated tablets are not interchangeable.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Levitra and Staxyn. 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 Levitra or Staxyn is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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

Levitra and Staxyn are indicated for the treatment of ED.

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Other Uses with Supportive Evidence

2. 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: 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]).

In an open-label study in 40 patients with Raynaud disease (33 patients with secondary and 7 patients with primary Raynaud disease), patients received Levitra 10 mg twice daily (BID) for 2 weeks.⁶ Levitra improved digital blood flow in 28 patients and 12 patients did not respond. Twenty-four of the 40 patients reported a reduction of the total daily duration of Raynaud disease-related attacks, and the number and severity of attacks were reduced in 50% and 53% of patients, respectively. The Raynaud condition score (RCS) declined from a mean of 5.05 ± 0.38 to 3.54 ± 0.31 ($P < 0.001$).

A double-blind, single-center, randomized, placebo-controlled, two-period, crossover study was conducted for 6 weeks using Levitra (10 mg BID) in patients ($n = 53$) with primary and secondary Raynaud Phenomenon.⁷ The RCS and digital blood flow were assessed as primary endpoints. Levitra significantly reduced RCS on average by -0.45 compared with placebo ($P = 0.03$). Compared with placebo, Levitra also decreased the number (-0.51 vs. placebo; $P = 0.005$) and cumulative duration of Raynaud attacks per day (-11.43 minutes vs. placebo; $P = 0.003$). There was also a non-significant improvement in the digital blood flow.

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) disease.⁸ 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.⁹ 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).

3. 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 Phase IIb, multicenter, parallel-group, double-blind trial, 222 men with lower urinary tract symptoms (LUTS) secondary to BPH with or without concomitant ED were randomized to Levitra 10 mg or placebo BID for 8 weeks.¹⁰ Patients had an International Prostate Symptom Score (IPSS) ≥ 12 (mean baseline score: 16.8). The primary efficacy parameters were the IPSS total score and the maximum urinary flow rate (Q_{max}) with 2.2 points difference in IPSS and 2 mL/sec in Q_{max} being significant. After 8 weeks there was a significant improvement in the IPSS total score for Levitra vs. placebo (-5.9 and -3.6, respectively; difference = 2.3; $P = 0.0013$). This improvement is comparable to those reported with α -blockers. Q_{max} did not change significantly with therapy, but baseline values

were already close to normal. Levitra therapy was associated with a nominally statistically significant improvement in erectile function (EF) compared to placebo.

A Phase III placebo-controlled study evaluated the efficacy of tamsulosin vs. tamsulosin plus Levitra in men with LUTS/BPH.¹¹ Patients (n = 60) were randomized to a 12-week treatment with Levitra 10 mg/day plus tamsulosin 0.4 mg/day or placebo and tamsulosin 0.4 mg/day. The primary endpoint was change from baseline to Week 2 and Week 12 of total IPSS score. Other subscores, including IPSS-both score (IPSS-B), overactive bladder short-form questionnaire (OAB-q), and International Index of Erectile Function (IIEF) domain 5 scores were also considered. Both at Week 2 and Week 12, treatment with tamsulosin plus Levitra resulted in a significant change in IPSS, IPSS-B, and OAB-q scores. After 12 weeks of Levitra, a significant increase in Q_{\max} and average urinary flow rate (Q_{ave}) was also noted.

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.¹² 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 Q_{\max} (-0.00; $P =$ not significant) 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.¹³ The guidelines add that based on the results from a meta-analysis¹¹, younger men with lower body mass index and more severe LUTS benefit the most from PDE5 inhibitors.

4. 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) Levitra or Staxyn is prescribed by or in consultation with an urologist.

Data from studies in humans using the PDE5 inhibitors, Viagra® (sildenafil tablets) or Levitra, are conflicting.¹⁴ Several small studies with Viagra given on a daily (QD) basis have been favorable, but a large trial with Levitra has suggested no benefit with daily dosing; however, a statistically significantly better outcome was noted with Levitra on-demand therapy compared with placebo.¹⁵

Levitra was studied in men following bilateral nerve-sparing radical prostatectomy in the largest study to date.¹⁵ In this double-blind, double-dummy, multicenter, parallel-group study, 628 men were randomized to placebo, nightly Levitra 10 mg, or on-demand Levitra (flexible dose starting with 10 mg and titrated to either 5 mg or 20 mg) for 9 months starting within 14 days after undergoing a bilateral nerve-sparing radical prostatectomy. Patients had normal preoperative erectile function with an IIEF-erectile function (EF) domain (IIEF-EF) score ≥ 26 at screening without the use of therapy or devices for improvement of erections. After the 9-month treatment period patients entered a 2-month single-blind placebo washout period where the dose of Levitra could be titrated by the investigator to preserve subject blinding. In the open-label period Levitra 10 mg (titrated to either 5 or 20 mg) on-demand was used. The primary efficacy variable was the percentage of patients with an IIEF-EF score ≥ 22 (mild ED) after the 2-month washout period using last observation carried forward (LOCF) analysis. In all, 423 patients finished the study. The primary efficacy variable was not met. There was no statistically significant difference between the treatment groups in the percentage of patients with IIEF-EF score \geq

22 at the end of washout; IIEF-EF scores ≥ 22 were attained in 28.9%, 24.1%, and 29.1% for placebo, Levitra nightly, and Levitra on-demand, respectively. At the end of the double-blind treatment period, the percentage of patients with IIEF-EF score ≥ 22 was statistically significantly better for Levitra on-demand vs. placebo ($P < 0.0001$): 24.8% (placebo), 32.0% (Levitra nightly), and 48.2% (Levitra on-demand). The efficacy of Levitra on-demand during the open-label phase was similar in all three study groups (i.e., regardless of the previous treatment).

The European Association of Urology (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.¹⁷ 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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Levitra or Staxyn have 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. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Pulmonary Arterial Hypertension (PAH). In a 1-year, open-label, multicenter study conducted in China, 45 patients with PAH who were able to walk a maximum of 550 meters in a 6-minute walk test (no minimum) received Levitra.¹⁸ At baseline 12% of patients were in World Health Organization (WHO) functional class IV; 64% of patients were in class III, and 24% of patients were in class II. Patients received Levitra 5 mg daily for one month and then 5 mg BID if no significant adverse effects occurred. Patients were reassessed at 3, 9 and 18 months. Mean baseline 6-minute walk distance (6MWD) was 409 ± 103 meters. The mean 6MWD increased by 70.7 ± 78.4 meters at 3 months ($P < 0.0001$) and 83.4 ± 91.8 meters at 14 ± 3 months. After 3 months, WHO functional class improved ($P < 0.0001$) and further improvement was noted at 14 ± 3 months ($P < 0.0001$ compared with baseline). At the end of the study, 11% of patients were in WHO class I, 69% of patients were in class II, 18% of patients were in class III, and 2% of patients were in class IV.

In a double-blind, placebo-controlled study, patients ($n = 66$) in China with PAH were randomized 2:1 to receive Levitra 5 mg QD for 4 weeks, followed by 5 mg BID or placebo for 12 weeks.¹⁹ After completing this phase, patients were treated with open-label Levitra (5 mg BID) for an additional 12 weeks. At Week 12, the mean placebo-corrected 6MWD was increased with Levitra by 69 meters (95% confidence interval [CI]: 41m, 91m; $P < 0.001$). This improvement was maintained in the extension-phase for a total of at least 24 weeks. There were also improvements in the mean placebo-corrected cardiac index, pulmonary arterial pressure and pulmonary vascular resistance (PVR) at Week 12. Larger, longer-term, randomized trials are needed to determine the safety and efficacy of Levitra in PAH. Revatio® (sildenafil tablets) and Adcirca® (tadalafil tablets) are indicated for the treatment of PAH.

2. 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 from 3 years 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 references to gender in indications. i.e., “(men or women)” from Raynaud’s Phenomenon and Pulmonary Arterial Hypertension. Deleted women with antidepressant-associated sexual dysfunction, female sexual-arousal disorder, premature ejaculation, and penile rehabilitation for erectile dysfunction of nonsurgical etiology from Conditions Not Recommended for Approval due to lack of any new data.	08/03/2016
Annual revision	No criteria changes	08/09/2017
Annual revision	No criteria changes	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>.