VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: Erectile Dysfunction – Cialis® (tadalafil tablets – Eli Lilly)

TAC APPROVAL DATE: 08/22/2018

OVERVIEW

Cialis, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5), is indicated for the treatment of erectile dysfunction (ED), the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH), and for the treatment of ED and the signs and symptoms of BPH (ED/BPH).[1] If Cialis is used with finasteride to initiate BPH treatment, such use is recommended for up to 26 weeks. This is because the incremental benefit of Cialis decreases from 4 weeks to 26 weeks, and the benefit beyond 26 weeks is unknown.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Cialis. 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 Cialis is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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

   Cialis is indicated for the treatment of ED, including in men with ED and concomitant benign prostatic hypertrophy (ED/BPH).[1]

2. **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, dutasteride).

Cialis is indicated for the treatment of the signs and symptoms of BPH, including men with ED/BPH.[1]
Note: For men with ED/BPH, use criterion 1 above.

Other Uses with Supportive Evidence

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: 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]).

   Limited information is available with the use of Cialis in Raynaud disease.[6-8]

   A small prospective, randomized, double-blind, placebo-controlled, crossover study evaluated Cialis at a dose of 20 mg QD for 4 weeks compared with placebo in women with Raynaud disease secondary to systemic scleroderma.[8] A total of 45 women enrolled in the trial, and 39 women completed the study. Treatment with Cialis showed no statistically significant difference in RCS, Raynaud frequency, or Raynaud duration compared with placebo.

   A double-blind, placebo-controlled, fixed-dose, crossover study evaluated the efficacy of Cialis in patients with scleroderma or mixed connective tissue disease (MCTD).[9] Patients experienced ≥ four Raynaud's attacks per week in the 2 weeks before study inclusion, despite treatment with vasodilators for ≥ 3 months. Patients were randomized to receive either Cialis 20 mg or matching placebo every other day for 6 weeks. All the patients were receiving calcium channel blockers; 18 patients were also on other vasodilators. A total of 24 patients completed the study. Cialis significantly improved the mean daily frequency and mean daily duration of Raynaud's phenomenon as compared with placebo and baseline, respectively. About 67% of the patients had > 25% improvement in the mean daily duration of Raynaud's phenomenon while receiving Cialis as compared with 25% of the patients who had > 25% improvement during placebo therapy. Cialis healed existing digital lesions and prevented development of new digital lesions. It also improved quality of life measures in patients with resistant secondary Raynaud's phenomenon.

   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.[10] 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% of experts would recommend Cialis 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.[11] 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. **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) Cialis is prescribed by or in consultation with an urologist.

   In a prospective, 12-month study, patients (n = 65) that underwent nerve-sparing radical prostatectomy were randomized to control without rehabilitation (Group 1) or Cialis 20 mg 3 days per week (Group 2).[12] In Group 1 there was a significant decrease in penile measurements at Month 3 compared with preoperative measurements. There was no significant difference in penile length between postoperative Month 6 and Month 12 for all measurements. In Group 2 there was a decrease in all measurements at Month 3 compared with baseline, but there was no significant difference for penile measurements.

   In a randomized, double-blind, double-dummy, placebo-controlled trial, men (n = 423) post-radical prostatectomy were randomized to receive Cialis 5 mg QD, Cialis on-demand, or placebo for 9 months.[13] The primary endpoint was to measure the IIEF-EF score (≥ 22) after a 6-week drug-free washout period (DFW), followed by a 3-month open-label Cialis QD period. The primary endpoint was not met since there was no statistically significant difference between the treatment and placebo groups during the DFW period; however, there was a statistically significant difference between Cialis QD dosing and placebo during the 9-month double-blind treatment period.

   A Phase IV, randomized, double-blind, double-dummy, three-arm, placebo-controlled, parallel group study evaluated the treatment outcomes with Cialis 5 mg QD, Cialis 20 mg on-demand, or placebo in patients who recently had bilateral nerve-sparing radical prostatectomy surgery (n = 422).[14] At the end of the 9-month double-blind period, 22.3% of patients treated with Cialis QD had achieved "back-to-baseline" IIEF-EF compared with 11.3% of patients treated with Cialis on-demand, and 7.8% of patients treated with placebo. But there were no sustained treatment effects on unassisted erectile function during the 6-week drug-free washout period. After 3 months of open-label treatment with Cialis QD, the proportion of patients with "back-to-baseline" IIEF-EF almost doubled in all three groups.

   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.[15] 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.

5. **Pulmonary Arterial Hypertension (PAH).** Approve for 1 year in patients who cannot use Adcirca because the dose is not available using Adcirca, that is, patients who are using 10 mg doses of Cialis. Patients using 20 mg or 40 mg of Cialis for PAH should use Adcirca.

   Adcirca contains the same active ingredient as Cialis and is indicated for the treatment of PAH.[16] Cialis is available in 2.5 mg, 5 mg, 10 mg, and 20 mg tablets. Adcirca is available as 20 mg tablets. The approved dose of Adcirca for PAH is 40 mg QD with dosage adjustments recommended for patients with renal impairment, hepatic impairment, and in those using ritonavir. Cialis has been used for PAH based on case reports and placebo-controlled, double-blind studies.[16-18] *Note:* PAH can be due to a variety of causes and is associated with many different conditions (e.g., Eisenmenger syndrome).

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, Viagra® [sildenafil tablets]) for treatment or prevention of HAPE.

   In a small double-blind study, 29 adult mountaineers with a history of HAPE were randomized to prophylactic Cialis 10 mg, dexamethasone 8 mg or placebo BID given during the ascent from 490 meters within 24 hours and during a stay for 2 nights at 4,559 meters.[19] Two patients who received Cialis developed severe acute mountain sickness on arrival at 4,559 meters and withdrew from the study; they did not have HAPE at that time. HAPE developed in 7 of 9 patients on placebo, in one of the remaining Cialis patients, and in none of the 10 patients on dexamethasone. Eight of 9 patients on placebo, 7 of 10 patients on Cialis, and 3 of 10 patients on dexamethasone had acute mountain sickness.

   A small open-label study assessed the efficacy of adding Cialis 20 mg QD to standard acetazolamide 125 mg BID and compared it with acetazolamide monotherapy for the prevention of severe high-altitude illness (HAPE or high-altitude cerebral edema).[20] A total of 51 patients completed the study; 24 patients in the Cialis group and 27 patients in the control group. Overall, 15.7% of the patients (n = 8/51) developed severe high-altitude illness, and the rates were significantly lower in the Cialis group compared with the control group (4.2% vs. 25.9%, respectively; odds ratio [OR] = 8.05; P = 0.03). A reduction in the incidence of HAPE in the Cialis group compared with the control group accounted for most of the difference (4.2% vs. 22.2%, respectively; p = 0.06).

   Published guidelines for the prevention of HAPE recommend nifedipine as the preferred pharmacologic treatment option in patients who have a history of HAPE.[21] Other pharmacologic therapies mentioned in the guidelines for the prevention and/or treatment of HAPE include Serevent, Cialis, Viagra, dexamethasone, or acetazolamide. A recent review article on acute high-altitude sickness notes that nifedipine 30 mg BID in a slow-release formulation, Cialis 10 mg BID, and dexamethasone 8 mg BID appear to be similarly effective in lowering pulmonary artery pressure and reducing the incidence of HAPE from approximately 70% to ≤ 10%.[22]

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Cialis 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.

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 ED. 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. Under Conditions Not Recommended for Approval, deleted female sexual arousal disorder, women with antidepressant-associated sexual dysfunction, premature ejaculation, cold complex regional pain syndrome, and penile rehabilitation for erectile dysfunction of nonsurgical etiology.	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; ED – Erectile dysfunction.