



CIGNA PHARMACY COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Oral Phosphodiesterase-5 Inhibitors for Erectile Dysfunction (Viagra[®], Levitra[®], Cialis[®])

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Alprostadil (Caverject[®], Edex[®], Muse[®])
 Oral Phosphodiesterase-5 Inhibitors for PAH (Revatio[®], Adcirca[®])
 Penile Prosthesis for Erectile Dysfunction
 Surgery for Male Sexual Dysfunction

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), 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 supercedes** 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. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

Note: Erectile dysfunction therapy is specifically excluded under most benefit plans. Please refer to the applicable benefit plan document to determine benefit availability and the terms and conditions of coverage.

If coverage is available for erectile dysfunction therapy, then:

Oral Phosphodiesterase-5 Inhibitor Therapy includes the following drugs:

- Sildenafil (Viagra[®])
- Vardenafil (Levitra[®])
- Tadalafil (Cialis[®])

CIGNA covers Oral Phosphodiesterase-5 Inhibitor Therapy as medically necessary for the treatment of male erectile dysfunction when ANY of the following criteria is met:

- age 60 or older
- hormonally-induced erectile dysfunction with **EITHER** of the following:
 - erectile dysfunction persists despite correction of an abnormal testosterone, prolactin, or thyroid level

- correction of the hormonal deficiency is contraindicated due to comorbidity (e.g., a low testosterone in a man with prostate cancer)
- neurogenic erectile dysfunction such as resultant from spinal cord injury, multiple sclerosis, cerebral vascular accident (CVA), diabetes, radical prostatectomy or surgically induced impotence
- vasculogenic erectile dysfunction such as resultant from aortic aneurysm, atherosclerosis, hypertension, hyperlipidemia, or peripheral vascular disease (PVD)
- pelvic trauma-induced erectile dysfunction such as resultant from compression injuries or radiation
- pharmacologic-induced erectile dysfunction where the patient has tried ONE alternate, non-erectile dysfunction-causing medication and erectile dysfunction persists, **OR** there is a contraindication to making medication changes

Note: Please see CP 6121 (Oral Phosphodiesterase-5 Inhibitors for PAH) for non-erectile dysfunction coverage.

FDA Approved Indication

Viagra, Levitra, and Cialis are all approved for the treatment of erectile dysfunction.

FDA Recommended Dosing

Viagra

For most patients, the recommended dose of sildenafil is 50 mg (dosage range includes 25 to 100 mg) taken, as needed, approximately one hour before sexual activity.

Levitra

Dosage range includes 5 to 20 mg taken once daily one hour before sexual activity.

Cialis

The recommended starting dose of tadalafil is 10 mg taken prior to anticipated sexual activity without regard to meals.

The FDA has approved tadalafil for once daily use (2.5 mg and 5 mg). When tadalafil is taken daily, men can attempt sexual activity at anytime between doses. In clinical trials, when taken without restrictions on the timing of sexual activity, tadalafil for once daily use improved erectile function over the course of therapy. The approval of tadalafil for once daily use was based upon the evaluation of the comprehensive data package for the daily dosing option. The data include results from three phase III randomized, double-blind, placebo-controlled studies. Men with ED who participated in these clinical studies and who took tadalafil 2.5 mg and 5 mg once daily without regard to their timing of sexual activity experienced improved erectile function compared with those taking placebo. The recommended starting dose of tadalafil for once daily use is 2.5 mg, taken at approximately the same time every day, without regard to timing of sexual activity or meals. The daily dose may be increased to 5 mg, based on individual efficacy and tolerability.

Drug Availability

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.

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.

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".

General Background

Pharmacology/Disease Overview

Sexual stimulation causes the release of nitric oxide from nerve endings and endothelial cells in the corpus cavernosum. Nitric oxide activates the enzyme guanylate cyclase resulting in increased synthesis of cyclic guanosine monophosphate (cGMP) in the smooth muscle cells of the corpus cavernosum. The cGMP leads to smooth muscle relaxation, allowing increased blood flow into the penis, resulting in an erection. The synthesis, degradation, and resulting tissue concentration of cGMP is regulated by phosphodiesterases. The most abundant phosphodiesterase in the corpus cavernosum is oral 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 have no effect in the absence of sexual stimulation.

The pharmacokinetics of tadalafil is different from the other agents because tadalafil has a longer half-life and retains efficacy for up to 36 hours. Patients may prefer tadalafil over the other agents for this reason.

Guidelines

There are two main categories of erectile dysfunction - psychogenic and organic. Organic causes may be vascular, neurologic, hormonal, medical, or pharmacological. According to the American Urological Association (AUA), the management of ED begins with the identification of organic comorbidities and psychosexual dysfunctions; both should be appropriately treated. Organic comorbidities include hypertension, atherosclerosis, hyperlipidemia, and diabetes mellitus. Additional risk factors for ED include neurologic disease (e.g. spinal cord injury, multiple sclerosis, cerebral vascular accident); pelvic, perineal, or penile trauma or surgery; pelvic radiation therapy; and endocrinopathy. For patients with a definite endocrinopathy, endocrine therapy for hypogonadism, hyperprolactinemia, and thyroid disorders is an appropriate intervention.

The PDE5I are recommended by the AUA as first-line therapy in patients with ED, unless contraindicated. Since limited data are available to suggest that efficacy differences exist between the individual PDE5I, treatment decisions must be based on other factors, including side effects, patient preference, and cost.

Premature ejaculation (PE) is considered to be one of the most common sexual dysfunctions in men. The AUA has treatment guidelines for premature ejaculation. PE often occurs with or is misinterpreted to be ED. It is important for the clinician to get a good patient history to distinguish PE from ED to delineate the sexual dysfunction the patient is experiencing. ED should be managed first before treating PE. Once PE is diagnosed, psychological, behavioral, and pharmacological therapies can be used. Treatment options should be discussed with the patient and partner. The benefit should outweigh the risk of therapy since PE is not life-threatening. Currently, no medications are labeled for the treatment of PE. The pharmacological options in the AUA guidelines include selective and non-selective serotonin reuptake inhibitors and topical therapies. The PDE5 inhibitors are not listed as treatment options in the AUA guidelines, but these have not been updated since 2004.

Ongoing Studies Hypertension

In this study, a novel long-acting phosphodiesterase 5 inhibitor, was evaluated in 133 patients with mild to moderate hypertension, randomized into 1 of 4 groups: placebo, 4 mg, 10 mg, and 20 mg titrated after 14 days of dosing to 40 mg. Study medication was administered once daily for 28 days. Ambulatory BP monitoring was used. There was a statistically significant decrease (compared with placebo) in mean daytime systolic BP on day 28 at the 10 and 20/40 mg doses (by approximately 5 and approximately 7 mm Hg, respectively). Changes in mean daytime diastolic BP corresponded with those in systolic BP. The magnitude of BP lowering was greater on day 1 than on days 14 and 28, but the response was sustained between days 14 and 28. There was a dose-related increase in plasma cGMP concentration (statistically significant at the 20/40 mg dose). There was an increased incidence of headaches at the 10 and 20/40 mg doses (22% and 21%, respectively, compared with 12% with placebo) and an increased incidence of dyspepsia/gastroesophageal reflux disease and musculoskeletal adverse events at the 20/40 mg dose. In conclusion, PF-00489791 causes a clinically meaningful and sustained BP lowering in patients with hypertension. It is generally safe and well tolerated at the clinically efficacious doses.

PDE5-I for Women

The role, if any, of sildenafil in the management of sexual dysfunction in women remains to be established. In an open-label study in a limited number of postmenopausal women with a history of sexual dysfunction, sildenafil 50 mg administered approximately one hour before planned sexual activity did not improve overall sexual function. Additional study in women with sexual dysfunction is needed.

Premature Ejaculation (PE)

No published trials have compared the PDE5 inhibitors with each other in this disease state. Four published trials are available for sildenafil but not the other PDE5 inhibitors, with both placebo and active comparators. One trial evaluated sildenafil, clomipramine, paroxetine, and sertraline in adult men with PE. The authors did not present between group comparisons and will not be discussed further. One published case series is also available for sildenafil but not the other PDE5 inhibitors.

Raynaud's Phenomenon

Raynaud's phenomenon (RP) is an important clinical feature of systemic sclerosis (SSc) for which consistently effective therapies are lacking. The study was designed to assess the safety, tolerability, and efficacy of tadalafil, a selective, long acting type V cyclic GMP phosphodiesterase (PDE-5) inhibitor, in this clinical syndrome. A prospective, randomized, double-blind, placebo-controlled, crossover study compared oral tadalafil at a fixed dose of 20 mg daily for a period of 4 weeks versus placebo in women with RP secondary to SSc. Thirty-nine subjects completed the study and were evaluable. There were no statistically significant differences in Raynaud Condition Score (RCS), frequency of RP episodes, or duration of RP episodes between treatment groups. Placebo response was a confounding factor. Tadalafil appears to be safe and well tolerated but lacks efficacy in comparison to placebo as a treatment for RP secondary to SSc.

Sexual Dysfunction Related to Antidepressant Medications

Depression itself can cause sexual dysfunction along with the drugs to treat depression. All antidepressants have the potential for causing sexual dysfunction in both men and women. Selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed and are reported to have some of the highest incidences of sexual dysfunction, up to 70% in some studies. The PDE5 inhibitors are being evaluated for sexual dysfunction due to antidepressants. No published trials have compared the PDE5 inhibitors with each other for use in patients with sexual dysfunction due to antidepressant medications. Several published placebo-controlled trials are available for sildenafil and two retrospective analyses are available for tadalafil. There are numerous case reports and case series showing improvement of sexual dysfunction with the PDE5 inhibitors, primarily with sildenafil use. There are no long term studies, just case series, evaluating the effects of PDE5 inhibitors on both the sexual dysfunction accompanying the antipsychotic medications and the underlying disease state.

Sexual Dysfunction Related to Antipsychotic Medications

As with antidepressant medication, the use of drug holidays, dose reduction, and change in medication has been tried to alleviate the symptoms but not evaluated in clinical trials. Concerns regarding the potential for relapse cannot be ruled out. Therefore, adding on medications even with their adverse effect profile may be the best option in this patient population. The PDE5 inhibitors may be an option for this patient population. No published trials have compared the PDE5 inhibitors with each other for use in patients with sexual dysfunction due to antipsychotic medications. One published placebo-controlled trial is available for sildenafil. There are 2 case reports published using sildenafil for antipsychotic related sexual dysfunction. No other PDE5 inhibitors have been evaluated for this use. There are no published data on the use of these PDE5 inhibitors in women having sexual dysfunction due to antipsychotic medication.

Adverse Reactions/Contraindications

Each PDE5I agent is similar with respect to adverse effects, contraindications, and efficacy. The most common adverse reactions include headache, dyspepsia, back pain, myalgia, nasal congestion, flushing, and pain in limb. The FDA informed healthcare professionals of reports of sudden decreases or loss of hearing following the use of PDE5I. In some cases, the sudden hearing loss was accompanied by tinnitus and/or dizziness. Medical follow-up on these reports was often limited which makes it difficult to determine if the loss of hearing was related to the use of one of the drugs, an underlying medical condition, other risk factors for hearing loss, a combination of these factors, or other factors. Any sudden loss of hearing or decrease in hearing, tinnitus, or dizziness with concomitant use of PDE5I should be immediately reported to a healthcare professional.

The PDE5I can potentiate the hypotensive effects of nitrates, alpha blockers, anti-hypertensives and/or alcohol. Therefore, PDE5I are contraindicated in patients who are using any form of organic nitrate, either regularly

and/or intermittently because of the risk of severe hypotension. Caution is advised when PDE5I are co-administered with alpha blocking agents and/or anti-hypertensives because both have vasodilatory effects and an additive effect on blood pressure lowering may be anticipated. Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported rarely in temporal relationship with the use of PDE5I. There have been rare reports of prolonged erections more than four hours and priapism (painful erections more than six hours in duration) for this class of compounds.

The longer half-life of tadalafil imposes increased risk for drug interactions in patients taking potent cytochrome P450 (CYP450) inhibitors.

Coding/Billing Information

Note: This section is not in use.

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