Medication Policy Manual **Policy No:** dru461

Topic: Viagra® 25 mg, 50 mg, 100 mg **Date of Origin:** June 1998

Committee Approval Date: June 9, 2017 **Next Review Date:** April 2018

Effective Date: July 1, 2017

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Administration of Contract

Sildenafil for impotence is generally a benefit not covered by member contracts regardless of medical necessity.

If sildenafil for impotence is a covered benefit, contract language will be applied to determine coverage (See Appendix V). Generally, contract language specifies one of the following types of coverage to determine when this medication policy is applicable.

Coverage Type	Maximum Quantity Already defined by Contract Language	Coverage is based on Medical Necessity	Medication Policy Applies
1.	Yes	No	No
2.	Yes	Yes	Yes
3.*	No	Yes	Yes

* This applies, but is not limited to benefit plans where contracts are silent on coverage of impotence treatments and/or impotence medications.

Note: For groups who fall under OAR 836-053-1405, this mandate takes precedence over any contract limitations.

Description

Sildenafil (Viagra) is an oral medication used for erectile dysfunction. This policy applies to formulations of sildenafil (Viagra) only.

Policy/Criteria

I. Most contracts require prior authorization approval of sildenafil (Viagra) for coverage. Sildenafil (Viagra) may be considered medically necessary for erectile dysfunction in men when the following criteria A and B below are met:

A. There is documented diagnosis of organic impotence.

AND

B. There is clinical documentation that includes an evaluation of reversible causes of impotence.

II. FOR GROUP MEMBERS IN OREGON WHO FALL UNDER OAR 836-053-1405: Sildenafil (Viagra) may also be considered medically necessary for erectile dysfunction in men when a licensed mental health practitioner has diagnosed sexual dysfunction as defined by the DSM-5 criteria (see Appendix I).

III. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx considers sildenafil (Viagra) to be a self-administered medication.

B. When prior authorization is approved, sildenafil (Viagra) may be authorized in quantities up to six tablets per month (or the maximum quantity specified in the contract).

C. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

IV. Sildenafil (Viagra) is considered not medically necessary when used for the following conditions:

A. Psychogenic impotence.

B. Impotence resulting from medication use.

C. Lower urinary tract symptoms (LUTS) resulting from benign prostatic hypertrophy (BPH).

D. Pulmonary arterial hypertension (PAH)

V. Sildenafil (Viagra) is considered investigational when used for all other conditions, including, but not limited to:

A. Use in combination with riociguat (Adempas) or treprostinil oral (Orenitram)

B. Achalasia.

C. Chronic obstructive pulmonary disease (COPD), with or without pulmonary hypertension.

D. Enhancing exercise performance.

E. Female arousal disorders.

F. Heart failure.

G. Males with a functioning penile prosthesis or post removal of prosthesis.

H. Preservation of penile function after radical prostatectomy.

I. Pulmonary hypertension (PH) WHO Groups 2-5 (See Appendix II), including PH associated with:

1. Left heart disease, including congestive heart failure (CHF) or valvular disorders

2. Lung diseases, including COPD and idiopathic pulmonary fibrosis (IPF)

3. Chronic thrombotic and/or embolic disease

4. Sarcoidosis

J. Raynaud's phenomenon.

Position Statement

Summary

ERECTILE DYSFUNCTION (ED) [1-6]

- The PDE-5 inhibitors [sildenafil, tadalafil, vardenafil (Levitra®), vardenafil ODT (Staxyn®) and avanafil (Stendra®)] are used to treat erectile dysfunction (ED).
- All PDE-5 inhibitors are effective for treatment of ED. There is no conclusive evidence of any difference in efficacy among the PDE-5 inhibitors in improving the quality or duration of erection in men with erectile dysfunction due to organic, psychogenic, or mixed causes, including diabetes mellitus.
- For the treatment of erectile dysfunction, generic sildenafil is the lowest-cost PDE-5 inhibitor and can be titrated to the optimal dose for each patient.
- Sildenafil has gained the most clinical data to support efficacy in many different patient subgroups, such as erectile dysfunction associated with angina, parkinsonism, spina bifida, spinal cord injury, ischemic heart disease, multiple sclerosis, kidney transplant recipients or chronic dialysis. Tadalafil and vardenafil have also been studied in different subpopulations.
- Daily dosing of PDE-5 inhibitors has not been shown to be superior to as needed dosing in the treatment of erectile dysfunction.
- Several studies demonstrate the efficacy of PDE-5 inhibitors in drug-induced (antidepressant and antipsychotic) erectile dysfunction. This use is considered not medically necessary, as treatment of the underlying cause of erectile dysfunction is the first-line of treatment (reversible cause).
- PDE-5 inhibitors are considered investigational when used for conditions for which there is poor to no available evidence of efficacy.

PULMONARY ARTERIAL HYPERTENSION (PAH)

- Pharmacologic treatment of PAH includes oral anticoagulants, diuretics, oxygen, inotropic agents (digoxin and dobutamine), calcium channel blockers, prostacyclin and prostacyclin analogs (PGEs) (epoprostenol, treprostinil, and iloprost), endothelin-receptor antagonists (ETAs) (ambrisentan, bosentan, macitentan), PDE-5 inhibitors (sildenafil, tadalafil), and riociguat (Adempas), a soluble guanylate cyclase (sGC) stimulator.

- Generic sildenafil is the lowest cost PDE-5 treatment option. Sildenafil 20mg three times daily has been shown to improve exercise tolerance in patients with arterial hypertension (PAH) when compared with placebo. Improved exercise tolerance has been correlated with improved survival in this population. [7,8]

Clinical Efficacy

ERECTILE DYSFUNCTION (ED) [2-6,9]

- Efficacy of PDE-5 inhibitors was based on ability to achieve and maintain erection sufficient for sexual activity.
- Assessments were made by patients from 4 weeks to 3 months.
- Overall, success rates with PDE-5 inhibitors were better than those achieved with placebo.
- Better results were generally achieved in patients with less impairment at baseline.

BENIGN PROSTATIC HYPERPLASIA (BPH)

- Tadalafil is the only PDE-5 inhibitor approved for the treatment of lower urinary tract symptoms (LUTS) in men with BPH. It can be used in men with or without concurrent erectile dysfunction.
- Tadalafil is intended to treat the signs and symptoms of BPH, and has not been shown to reduce the risk of urinary retention or the need for surgery. The 5-alpha reductase inhibitors [e.g. finasteride, dutasteride] have been shown to reduce these risks. [10]
- Change in LUTS in BPH is measured by International Prostate Symptom Score (IPSS), a subjective, 7-item recall questionnaire with a maximum total score of 35 points. Higher scores represent more severe symptoms of BPH. [10]
- Trials of both vardenafil [11] and sildenafil [12] in men with BPH with or without erectile dysfunction showed improvement in total IPSS from baseline by 1.7 to 4 points more than placebo, however clinical relevance of this improvement is unknown. Therefore, the use of vardenafil or sildenafil for BPH is considered not medically necessary.
- The efficacy of tadalafil, nor any PDE-5 inhibitor, relative to other treatments for BPH, such as alpha-1 adrenergic blockers (e.g. doxazosin, tamsulosin) and 5-alpha reductase inhibitors [e.g. finasteride, dutasteride], is unknown. [10]

OTHER CONDITIONS

- PDE-5 inhibitors are considered investigational for conditions for which there is poor or no available evidence of efficacy:
    * There is no reliable evidence to support the efficacy of PDE-5 inhibitors in the treatment of achalasia or female arousal disorders.
    * One small (n=10) Phase 2, placebo-controlled, cross-over trial of sildenafil found no beneficial effect on exercise capacity in COPD patients without pulmonary hypertension. Sildenafil significantly worsened oxygenation (gas-exchange), symptoms, and quality of life. [13]

* Although one small study in healthy adults suggests potential efficacy of sildenafil to enhance exercise performance in otherwise healthy individuals at low or high altitude [14], another small trial found no significant effect on pulmonary artery systolic pressure and possible worsening of symptoms of acute mountain sickness. [15]

* There are two small published trials that studied sildenafil in the management of heart failure with reduced ejection fraction. [16,17] Potential benefit was based on cardiopulmonary exercise testing parameters and hemodynamics (intermediate endpoints) and not clinical outcomes. One larger trial in heart failure patients with preserved ejection fraction, sildenafil did not significantly improve exercise capacity or clinical status. [18] Additional trials are needed to establish benefit in management of heart failure.

* A single, double-blind, placebo-controlled trial of 180 adults with idiopathic pulmonary fibrosis (IPF) suggested that sildenafil may improve oxygenation, and some quality of life parameters, but did not improve exercise capacity (walk distance) at 12-weeks based on a 20% improvement in the six-minute walk test compared to placebo. Effect on dyspnea was unclear. Overall functional status and survival were not evaluated. A previous smaller trial (n=29) found similar results. [19,20]

* Several studies support the efficacy of PDE-5 inhibitors in men with erectile dysfunction after undergoing bilateral nerve sparing radical retropubic prostatectomy.[21-32] Although some patients were able to achieve an erection with these agents, there is no reliable evidence that these agents preserve penile erectile function after prostate resection.

    - Evidence was not reliable due to flaws that included: retrospective or open label design; lack of randomization, control groups, blinding, and/or intent-to-treat analysis; small numbers of patients, high-dropout rates, and short duration of study.

- PDE-5 inhibitors have been used in a small number of patients with Raynaud's phenomenon to improve peripheral blood flow. Evidence is preliminary. Larger, well-controlled trials are necessary to establish the efficacy and safety of these medications in this disease. [33-35]

    * Two small placebo-controlled, cross-over studies evaluated sildenafil (n=18) and tadalafil (n=50) inpatients with Raynaud's phenomenon that was resistant to conventional vasodilatory treatment.[34,35] Frequency and duration of attacks was significantly lower in both the sildenafil and tadalafil treated groups. There was also improvement in digital ulcerations in several of the sildenafil-treated patients and ulcer healing reported in all of the tadalafil-treated patients with digital ulcers at baseline.

    - One small Phase II, placebo-controlled, cross-over study (n = 50) evaluated vardenafil in patients with primary or secondary Raynaud's phenomenon, resistant to conventional vasodilatory treatment. Despite a significantly greater decrease in frequency, duration and severity of Raynaud's symptoms in the vardenafil group, there was no significant difference in digital blood flow. Clinical outcomes, such as digital ulceration or amputation, were not reported. [36]
    - Larger, well-controlled trials are needed to establish the safety and effectiveness of PDE-5 inhibitors in the treatment of Raynaud's.
- No randomized, controlled trials have been published evaluating the use of sildenafil in patients with sarcoidosis.

Safety [37]

- All PDE-5 products carry similar product safety labeling that includes the contraindication for use in patients on nitrates and warnings about their use in patients on nitrates and alpha-adrenergic inhibitors.
    - Patients on nitrates were excluded from the clinical trials because of an interaction with sildenafil that results in hypotension.
- Headache, dyspepsia and back pain are the predominant adverse effects reported among all PDE-5 inhibitors.
- Safety data for sildenafil 20 mg in the treatment of PAH is limited to adverse events described in the 12-week pivotal trial and an open-label extension trial up to one year.
- Co-administration of PDE5s with nitrates in any form is contraindicated.
- Co-administration of sildenafil with potent CYP3A4 inhibitors (see *Appendix III*) may substantially increase serum levels of sildenafil and is not recommended.
- Use of riociguat with any phosphodiesterase inhibitor (e.g. sildenafil, tadalafil, dipyridamole, or theophylline) is contraindicated due to excessive hypotension in combination.

Dosing and administration [37]

ERECTILE DYSFUNCTION

- Avanafil, sildenafil and vardenafil doses need to be given between 0.4-4 hours prior to sexual intercourse to be effective.
- Tadalafil has a longer half-life and in clinical trials has shown to improve erectile dysfunction compared to placebo up to 36 hours following dosing, allowing a longer window (36 hours) opportunity or "full day" coverage for intercourse to occur.
- Dose titration is used to find the optimal PDE-5 inhibitor dose for each patient. Sildenafil (Viagra) is available as 25 mg, 50 mg, and 100 mg tablets. Generic sildenafil (generic Revatio) is available as 20 mg tablets and significantly less costly than all the branded PDE-5 inhibitors. Because all PDE-5 inhibitor doses are titrated to effect, lowest-cost generic sildenafil 20 mg tablets will be adequate for most patients.

PULMONARY ARTERIAL HYPERTENSION

- The recommended dose of sildenafil for the treatment of PAH is 20 mg orally three times per day.
- No additional benefit is observed above the recommended dose.

Cross References
Advanced Therapies for Pharmacologic Treatment of Pulmonary Hypertension, BlueCross BlueShield Association Medical Policy, 5.01.09, Issue 3.2015.
Adempas®, riociguat dru322
bosentan-containing medications, Tracleer®, Medication Policy Manual, dru218
High cost drugs with lower cost alternatives, dru420
Letairis ®, ambrisentan dru219
Levitra®, Staxyn®, vardenafil dru096
Opsumit, macitentan dru324
Orenitram, treprostinil oral tablets dru337
Remodulin®, treprostinil injectable dru222
Stendra™, avanafil dru277
tadalafil-containing medications, Cialis®, Adcirca® dru184
Tyvaso®, treprostinil inhalation dru221
Ventavis®, iloprost inhalation dru220

Codes	**Number**	**Description**
In-house	J031	Viagra
BCBSA	S0090	Sildenafil citrate (Viagra), 25 mg
ICD-10	N52.9	Impotence of organic origin.
ICD-10	N40.0	Hyperplasia (benign) of the prostate (BPH).

Appendix I: DSM-5 Recognized Sexual Dysfunctions

Codes	Number	Description
ICD-10	F52.32	Delayed Ejaculation
ICD-10	F52.21	Erectile Disorder
ICD-10	F52.0	Male Hypoactive Sexual Desire Disorder
ICD-10	F52.8	Other Specified Sexual Dysfunction
ICD-10	F52.9	Unspecified Sexual Dysfunction

Appendix II: Investigational Indications for Sildenafil - Revised WHO Classification of PH – Groups 2-5 [38]

Group 2. Pulmonary hypertension with left heart disease
- Left-sided atrial or ventricular heart disease (systolic dysfunction, diastolic dysfunction)
- Left-sided valvular heart disease

Group 3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
- Chronic obstructive pulmonary disease (COPD)
- Interstitial lung disease (e.g. idiopathic pulmonary fibrosis)
- Sleep disordered breathing (e.g. obstructive sleep apnea (OSA))
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

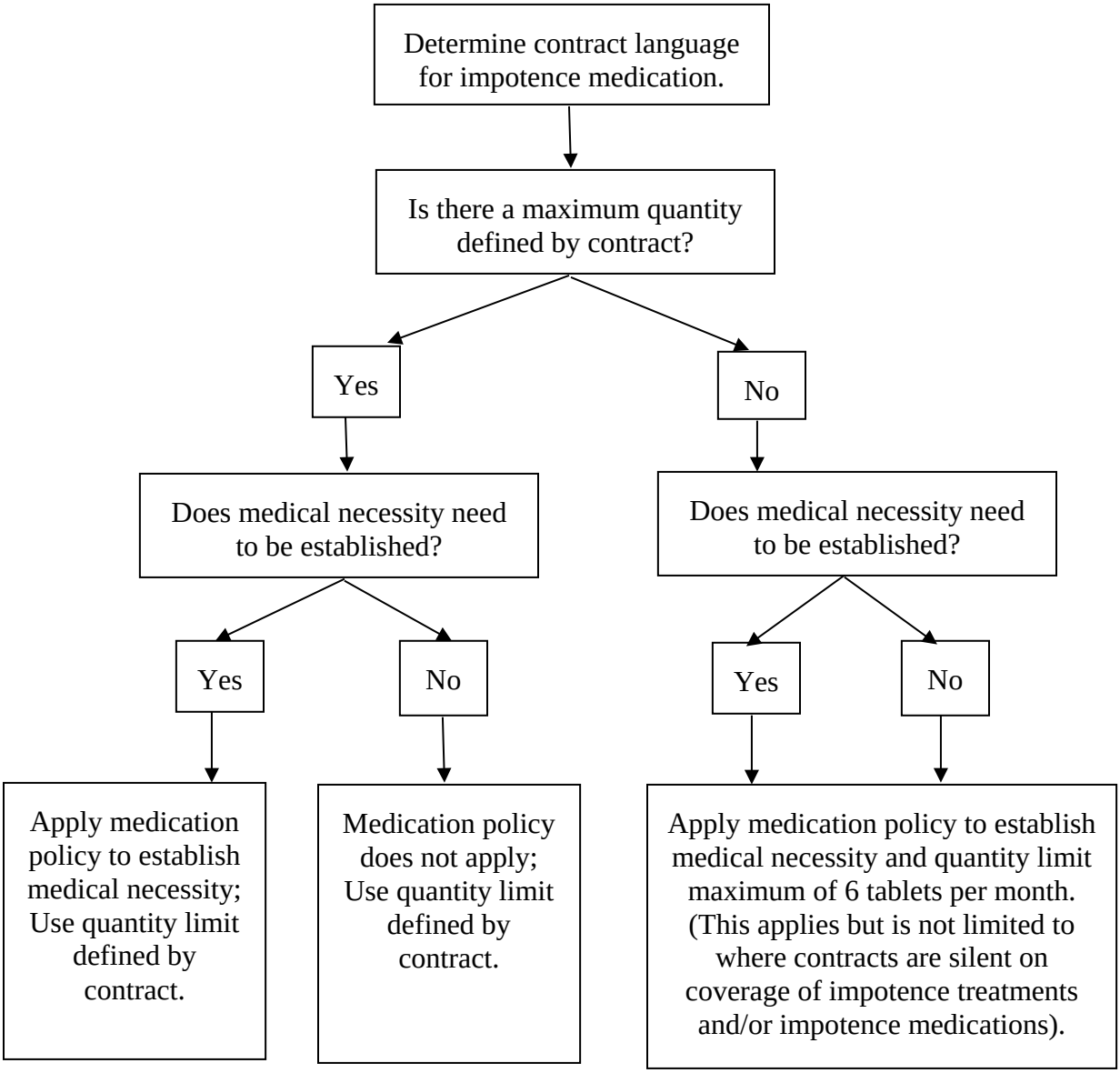
Group 4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease (CTEPH)
- Thromboembolic obstruction of proximal pulmonary arteries
- Thromboembolic obstruction of distal pulmonary arteries
- Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)

Group 5. Miscellaneous
- Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

Appendix III. Vasoactive alternatives for treatment of Raynaud's phenomenon and digital ulcers [39]
Calcium channel blockers (i.e. amlodipine, diltiazem, nifedipine)
Renin-angiotensin inhibitors [angiotensin-converting enzyme inhibitors (i.e. enalapril, lisinopril) or angiotensin II receptor blockers (ARBs) (i.e. losartan, olmesartan (Benicar®), telmisartan (Micardis®)]

Appendix IV

Impotence Medications - Administration of Contract Language and Medication Policy



Note: For fully insured members in Oregon, OAR 836-053-1405 takes precedence over any contract limitations.

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Revision History

Revision Date	Revision Summary
6/9/2017	No criteria changes with this annual update.
6/10/2016	New policy.