IMPORTANT REMINDER

This Medical 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 medical policy is to provide a guide to coverage. Medical 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

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

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

<table>
<thead>
<tr>
<th>Coverage Type</th>
<th>Maximum Quantity Already defined by Contract Language</th>
<th>Coverage is based on Medical Necessity</th>
<th>Medication Policy Applies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3.*</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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

Description

Vardenafil is an oral medication used for erectile dysfunction.
Policy/Criteria

I. Most contracts require prior authorization approval of vardenafil for coverage. Vardenafil 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 (ICD-9 - 607.84).

   AND

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

II. Administration, Quantity Limitations, and Authorization Period

   A. OmedaRx considers vardenafil to be a self-administered medication.

   B. When prior authorization is approved, vardenafil may be authorized in quantities of 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.

III. Vardenafil 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).

IV. Vardenafil is considered investigational when used for all other conditions, including but not limited to:

   A. Achalasia.

   B. Continence recovery after prostatectomy.

   C. Enhancing exercise performance.

   D. Female arousal disorders.

   E. Heart failure.

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

   G. Preservation of penile function after radical prostatectomy.

   H. Pulmonary arterial hypertension.

   I. Raynaud’s phenomenon.

   J. Tinnitus.
Position Summary

- The PDE-5 inhibitors [sildenafil, tadalafil, vardenafil (Levitra®), vardenafil ODT (Staxyn®) and avanafil] are used to treat erectile dysfunction (ED). [1-5]

- 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. [6]

- 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. [6] Tadalafil and vardenafil have also being studied in different subpopulations.

- Sildenafil, available as Revatio®, and tadalafil, available as Adcirca®, are also FDA-approved for the treatment of pulmonary arterial hypertension (PAH) to improve exercise ability. [7,8]

- Daily dosing of PDE-5 inhibitors has not been shown to be superior to as needed dosing in the treatment of erectile dysfunction. [6]

- Several studies demonstrate the efficacy of PDE-5 inhibitors in drug-induced (antidepressant and antipsychotic) erectile dysfunction. [6] 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.

Clinical Efficacy

ERECTILE DYSFUNCTION (ED)

- Efficacy of PDE-5 inhibitors was based on ability to achieve and maintain erection sufficient for sexual activity. [1-5]

- Assessments were made by patients from 4 weeks to 3 months. [1-5]

- Overall, success rates with PDE-5 inhibitors were better than those achieved with placebo. [1-6]

- Better results were generally achieved in patients with less impairment at baseline. [6]

PULMONARY ARTERIAL HYPERTENSION (PAH)

- Two PDE-5 inhibitors, sildenafil and tadalafil, have been studied in, and are approved to improve exercise ability in patients with pulmonary hypertension. [7,8] There is insufficient evidence to support the use of vardenafil in this population.[9]

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. [5]

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 [11,12] and sildenafil [13] 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 (Avodart)], is unknown. [10]

OTHER CONDITIONS

- PDE-5 inhibitors are considered investigational for conditions for which there is poor or no available evidence of efficacy.

  * A small trial studied vardenafil in continence recovery after bilateral nerve sparing prostatectomy. This study was preliminary and only recruited 39 patients. Larger studies are necessary to establish a role for vardenafil in this condition. [14]

  * 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. [15-18]

    - 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 [18]

    - Larger, well-controlled trials are needed to establish the safety and effectiveness of PDE-5 inhibitors in the treatment of Raynaud’s.

  * In a small (n = 42) exploratory study, vardenafil was not found to improve symptoms of tinnitus when compared with placebo. [19]

  * There is no evidence to support the use of vardenafil in any other conditions, including, but not limited to, achalasia, female arousal disorders, heart failure, or for exercise performance.
Safety

- 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. [1-5,7,8]
  
  * 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. [1-5,7,8]

Dosing and administration [1-5,7,8]

- Avanafil, sildenafil and vardenafil doses need to be given between 0.4-4 hours prior to sexual intercourse to be effective. [1-4]

- 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. [5]

- 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. [2,7] Because all PDE-5 inhibitor doses are titrated to effect, lowest-cost generic sildenafil 20 mg tablets will be adequate for most patients.

Cross References

tadalafil-containing medications, Adcirca®, Cialis®, Medication Policy Manual, dru184
sildenafil-containing medications, Revatio®, Viagra®, Medication Policy Manual, dru117

Stendra®, avanafil, Medication Policy Manual, dru277

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ICD-9</td>
<td>607.84</td>
<td>Impotence of organic origin.</td>
</tr>
<tr>
<td>ICD-9</td>
<td>600.0</td>
<td>Hyperplasia (benign) of the prostate (BPH).</td>
</tr>
</tbody>
</table>

References

5.  Cialis® (tadalafil) prescribing information, Eli Lilly and Company: Indianapolis, IN; April 2014.

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8. Adcirca® (tadalafil) prescribing information. Eli Lilly & Company: Indianapolis, IN; April 2015.
Appendix 1
Impotence Medications - Administration of Contract Language and Medication Policy

Determine contract language for impotence medication.

Is there a maximum quantity defined by contract?

Yes
Does medical necessity need to be established?

Yes
Apply medication policy to establish medical necessity; Use quantity limit defined by contract.

No
Medication policy does not apply; Use quantity limit defined by contract.

No
Apply medication policy to establish medical necessity and quantity limit maximum of 6 tablets per month. (This applies but is not limited to where contracts are silent on coverage of impotence treatments and/or impotence medications).

No
Does medical necessity need to be established?

Yes
No