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## Erectile Dysfunction Agents Step Therapy Criteria

**NOTE:** This step therapy (ST) criteria contains a quantity limit of 8 tablets total for any combination of the 3 oral products (Viagra/sildenafil, Cialis/tadalafil, or Levitra/vardenafil) or a quantity limit of 8 units total for any combination of the 3 non-oral alprostadil products (Caverject, Edex, alprostadil, Muse).

Brand	generic	Dosage Form
Caverject®	alprostadil	injection
Cialis®	tadalafil	oral tablet
Edex®	alprostadil	injection
Levitra®	vardenafil	oral tablet
Muse®	alprostadil	urethral suppository
Viagra®	sildenafil	oral tablet

### PROGRAM OBJECTIVES

The intent of the step therapy (ST) criteria for the Erectile Dysfunction (ED) Agents Step Therapy Program is to ensure appropriate use of these agents. These criteria consider therapy with an ED agent appropriate when the patient has been diagnosed with primary erectile dysfunction or impotence and if the erectile dysfunction is secondary to an organic comorbidity such as vascular insufficiency, diabetes mellitus, or prostate cancer. If an antidiabetic medication or an oral antiandrogen to treat prostate cancer is found in the claims database, then the ED agent will pay automatically. These criteria include a quantity limit of 8 tablets total for any combination of the 3 oral products (sildenafil, tadalafil, or vardenafil) or a quantity limit of 8 units total for any combination of the 3 non-oral alprostadil products (Caverject, Edex, alprostadil injection, Muse). Requests for erectile dysfunction agents when step therapy criteria are not met will be reviewed through the manual review process. Use of an ED agent for treatment of ED secondary to prescription or recreational drug use or for lifestyle enhancement will not be considered approvable by these criteria. When ED agents are not a covered benefit, when members are designated as female, or when members are less than eighteen years of age, requests will be directed to the health plans for determination of coverage.

### SUMMARY OF STEP THERAPY PROGRAM

An ED agent will be approved when ALL of the following are met:

1. ED agents are a covered benefit for the patient **AND**
2. The patient is a male patient eighteen years of age and older

AND ONE of the following is met

1. A claim for a prerequisite agent (antidiabetic medication, oral antiandrogen to treat prostate cancer) with a days supply that begins or ends in the 90 days prior to the ED agent prescription is found in the prescription claims database **OR**
2. A manual request is submitted and ONE of the following criteria is met:
  - Patient has a medication history of an antidiabetic medication or an oral antiandrogen to treat prostate cancer that is not seen in the prescription claims database **OR**
  - Patient has a diagnosis of erectile dysfunction or impotence secondary to an organic etiology (e.g., diabetes, prostate cancer, vascular insufficiency) **AND** the physician has submitted documentation to support the use of and ED agent for the patient

Limits:

1. The criteria will not approve two ED agents concurrently.
2. The criteria contains a quantity limit of 8 tablets total for any combination of the 3 oral products (sildenafil, tadalafil, or vardenafil) or a quantity limit of 8 units total for any combination of the 3 non-oral alprostadil products (Caverject, Edex, alprostadil injection; Muse urethral suppository).

**PROGRAM FUNCTIONALITY**

**Electronic Edits**

The overall process for step therapy requires that another drug or drugs be tried in a specific previous time period before the claim drug. If the patient has met any of the requirements outlined below, the requested step therapy medication will be paid under the patient’s current prescription benefit. If the patient has not met the requirements, the system will reject with the message indicating that prior authorization is necessary. The Prior Authorization (PA) Criteria for Approval would then be applied to requests submitted by the patient’s practitioner for evaluation.

**Table 1: Summary of Erectile Dysfunction Step Therapy**

Targeted Agent(s)	Cialis (tadalafil), Levitra (vardenafil), Viagra (sildenafil); Caverject, Edex, Muse, alprostadil
Is auto-grandfathering implemented? (with look-back time frame)	N
Prerequisite Agent(s)	Any antidiabetic medication, including oral agents metformin, sulfonylureas, thiazolidinediones, alpha glucosidase inhibitors, meglitinides, DPP-4 inhibitors, any combination of these oral medications; injectable agents, including insulins, Byetta (exenatide), Symlin (pramlintide) OR Any oral antiandrogen medication used to treat prostate cancer, including flutamide, Casodex (bicalutamide), Nilandron (nilutamide)
Number of prerequisites required	1
Prerequisite look-back time frame	90 days <sup>a</sup>
Age-related edit?	Applies to male patients 18 years of age or older; these agents are not covered for
Additional comments	Criteria contains a quantity limit of 8 tablets total for any combination of the 3 oral products (sildenafil, tadalafil, or vardenafil) or a quantity limit of 8 units total for any combination of the 3 non-oral alprostadil products (Caverject, Edex, alprostadil injection; Muse urethral suppository).  Only one ED agent will be covered at a time.

a - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30 day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

**Table 2: Details of Erectile Dysfunction Step Therapy**

Targeted Agents	GPIs (multisource code)	Prerequisites	GPIs (multisource code)	Look-back Time frames
<b>ANY ONE of:</b> Cialis, Levitra, Viagra; alprostadil, Caverject, Edex, Muse	403040***** 40303010***** (M, N, O, or Y)	<b>ANY ONE of:</b> Antidiabetic agent, oral or injection OR Casodex, bicalutamide, flutamide, Nilandron	27***** (M, N, O, or Y) OR 214924***** (M, N, O, or Y)	90 days <sup>a</sup>

a - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30 day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

## Prior Authorization Criteria for Approval

The Prior Authorization (PA) Criteria for Approval provide a manual review process for claims that do not meet the electronic edit criteria and are not automatically paid. The criteria for approval through the PA process are identical to those set up in the electronic edit. The intent of the PA Criteria for Approval for erectile dysfunction agents is to ensure that patients who do not have history of prerequisite agents in the prescription claims database have the option of treatment with an ED agent. Approval will be given to patients who have a history of use of a prerequisite agent outside of the 90-day look-back period or outside of the current benefit plan. ED agents may also be approved if the physician has submitted documentation of a medical diagnosis of erectile dysfunction or impotence secondary to an organic etiology to support of the use of an ED agent in the patient.

### ***Erectile Dysfunction Agents***

#### **Initial and Renewal Evaluation**

1. Is the patient at least 18 years of age and male, and the requested agent is covered under their benefit plan?  
If yes to all requirements, continue to 2.  
If no to any requirement, forward to plan for benefit determination.
2. Does the patient's medication history indicate previous use of an antidiabetic medication or an oral antiandrogen used to treat prostate cancer (see Tables 1 and 2)?  
If yes, approve for 12 months. If no, continue to 3.
3. Does the patient have a diagnosis of erectile dysfunction or impotence secondary to an organic (not medication) etiology (e.g., diabetes, prostate cancer, vascular insufficiency)?  
If yes, continue to 4. If no, deny.
4. Has the prescriber submitted and the pharmacist reviewed documentation in support of the use of the requested agent for the intended diagnosis?  
If yes, pharmacist must review and may approve for 12 months based on review of information provided.  
If no, deny.

**NOTE:** These PA criteria will approve a quantity of 8 tablets total for any combination of the 3 oral products (Viagra/sildenafil, Cialis/tadalafil, or Levitra/vardenafil) or a quantity of 8 units total for any combination of the 3 non-oral alprostadil products (Caverject, Edex, alprostadil injection, Muse urethral suppository).

## **CLINICAL RATIONALE**

Once ED has been diagnosed and the underlying causes have been treated, the American Urological Association (AUA) in a 2006 guideline recommends treatment with an oral phosphodiesterase type 5 (PDE5) inhibitor (sildenafil, tadalafil, or vardenafil) as first-line therapy, unless contraindicated.<sup>7</sup> Other options include intra-urethral alprostadil, intracavernous vasoactive drug injection, vacuum constriction devices, and penile prosthesis implantation.<sup>7</sup>

The PDE5 inhibitors also have an inhibitory effect on PDE6, located in the rod and cone photoreceptors of the eye. Studies in mice indicate that sildenafil has a significant impact on retinal function and may have an impact on human carriers of retinosa pigmentosa.<sup>8</sup> There is no controlled clinical data evaluating the safety and efficacy of the PDE5 agents in patients with retinitis pigmentosa.<sup>4,6</sup> This group of patients has been excluded from PDE5 efficacy and safety trials. Use in patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, is not recommended.

The PDE5 agents have not been evaluated in patients with bleeding disorders or significant active peptic ulcers.<sup>2,4,6</sup> Although these agents have not been shown to increase bleeding times in healthy people, use in patients with bleeding disorders or significant peptic ulceration should be based upon careful risk-benefit assessment and used with caution.<sup>2</sup>

The oral PDE5 ED medications are contraindicated in patients who are taking organic nitrates or nitric oxide due to potentiation of hypotensive effects.<sup>2,4,6</sup> Patients prescribed these agents should not receive ED agents.

All three of the oral PDE5 agents interact with alpha blocking agents to some degree and treatment with an alpha antagonist and all doses of vardenafil and tadalafil as well as 50 mg and 100 mg doses of sildenafil should be administered with caution.<sup>7</sup> Prescribing information for PDE5 agents do not list concomitant alpha-blocker use as a contraindication but do recommend that for patients on alpha-blockers, the PDE5 agents should be started only when the patients are stable on alpha-blocker therapy and that they should be started on the lowest PDE5 dose. In those patients already taking an optimized dose of a PDE5 inhibitor, alpha-blocker therapy should be initiated at the lowest dose. Safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and other anti-hypertensive drugs.<sup>2,4,6</sup>

Current AUA guidelines do not recommend the use of testosterone or other androgens for the treatment of erectile dysfunction in patients with normal testosterone levels. However, men with hypogonadism have a reduced response to PDE5 inhibitors and treatment with testosterone has been shown to improve the response to sildenafil in men with erectile dysfunction with initially low serum testosterone levels.<sup>9-10</sup>

The use of alprostadil is contraindicated in patients with anatomical deformation of the penis, such as angulation, cavernosal fibrosis, or Peyronie's disease.<sup>1-6</sup> Alprostadil is contraindicated for patients with penile implants also.<sup>1,5,6</sup> Use of alprostadil urethral suppositories has not been evaluated in patients with implants.<sup>5</sup> If used, the PDE5 inhibitors should be used with caution in patients with anatomical deformation of the penis.<sup>2,4,6</sup>

The safety and efficacy of erectile dysfunction agent combinations has not been extensively studied.<sup>1-6,12,13</sup> Small studies evaluating alprostadil combined with a PDE5 agent report response rates of ninety-two to one hundred percent in patients who did not respond to oral sildenafil alone.<sup>11</sup> Double blind randomized controlled clinical trials are needed to establish benefits, optimal dosage, and possible adverse effects before combination therapy can be recommended.

## **FDA APPROVED INDICATIONS<sup>1-6</sup>**

*The following information is taken from individual drug prescribing information and is provided here as background information only. Not all FDA-approved indications may be considered medically necessary. All criteria are found in the section "Prior Authorization (PA) Criteria for Approval."*

### **Cialis<sup>2</sup>, Levitra<sup>4</sup>, Viagra<sup>6</sup>**

Cialis (tadalafil), Levitra (vardenafil), and Viagra (sildenafil) are indicated for the treatment of erectile dysfunction.

### **Caverject<sup>1</sup>**

Caverject (alprostadil) is indicated for the treatment of erectile dysfunction due to neurogenic, vasculogenic, psychogenic, or mixed etiology. Intracavernosal Caverject is also indicated as an adjunct to other diagnostic tests in the diagnosis of erectile dysfunction.

### **Edex<sup>3</sup>**

Edex (alprostadil) is indicated for the treatment of erectile dysfunction due to neurogenic, vasculogenic, psychogenic, or mixed etiology.

### **Muse<sup>5</sup>**

Muse (alprostadil) is indicated for the treatment of erectile dysfunction. Studies that established benefit demonstrated improvements in success rates for sexual intercourse compared with similarly administered placebo.

## REFERENCES

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### Document History

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