PRIOR AUTHORIZATION POLICY

POLICY: Alprostadil for injection
- Caverject® (alprostadil for injection – Pharmacia & Upjohn)
- Caverject Impulse® (alprostadil for injection – Pharmacia & Upjohn)
- Edex® (alprostadil for injection – Actient Pharmaceuticals)
- MUSE® (alprostadil urethral suppository – Vivus, Inc.)

TAC APPROVAL DATE: 11/11/2015; selected revision 12/02/2015

LAY CRITERIA EFFECTIVE DATE: 12/17/2015

OVERVIEW

Alprostadil belongs to the family of prostaglandins (specifically prostaglandin E_1 [PGE_1]), which are naturally occurring lipids with various pharmacological effects, including vasodilation and inhibition of platelet aggregation.[1-4] They are naturally present in the seminal vesicles and cavernous tissues of males.[5] As a smooth muscle relaxant, alprostadil has demonstrated efficacy for the treatment of erectile dysfunction (ED). It binds to specific receptors in the human penile tissue, and induces erection by relaxation of trabecular smooth muscle and by dilation of cavernous arteries.[3] This leads to an expansion of the lacunar spaces and entrapment of blood by compressing the venules, a process referred to as the corporal veno-occlusive mechanism.

The available injectable alprostadil products are: Caverject, Caverject Impulse (disposable, single-dose, dual chamber syringe system), and Edex. MUSE is a single-use, medicated transurethral system for the delivery of alprostadil directly in the urethra.[4] It is suspended in polyethylene glycol and is formed into a medicated pellet. MUSE is administered by inserting the applicator stem into the urethra after urination. All of the alprostadil products are indicated for the treatment of ED due to neurogenic, vasculogenic, psychogenic, or mixed etiology.[1-4] Additionally, intracavernosal Caverject may be used adjunct to other diagnostic tests in the diagnosis of ED.[1]

Clinical Efficacy

Erectile Dysfunction

There are very limited head-to-head comparative data available regarding the use of alprostadil for the treatment of ED. In their respective clinical studies, Caverject and Edex were found to be significantly more effective than placebo for the treatment of ED.[1-3] The mean duration of erection for Caverject ranged from 12 minutes for the lowest dose to about 71 minutes for the higher doses.[2] There was no placebo response in these studies. The efficacy of Caverject and Caverject Impulse, which includes an inactive excipient (alpha cyclodextrin), was shown to be comparable, as assessed by the erectile function domain score. The MUSE system was evaluated in placebo-controlled trials in doses ranging from 125 mcg to 1,000 mcg.[4] Couples using active therapy were more likely to have at least one successful sexual intercourse compared with patients treated with placebo (65% vs. 19%, respectively). The duration of erections sufficient for intercourse was 6 minutes with placebo compared with 16 minutes on MUSE.

Prophylaxis after Radical Prostatectomy (early penile rehabilitation)
The gold standard for the treatment of localized prostate cancer is radical prostatectomy (RP).[6] One of the complications of RP, even with improved surgical techniques such as nerve-sparing RP, is ED. The proportion of patients with ED post-RP is reported to be as high as 80% to 85%.[7] The treatments most studied for penile rehabilitation are alprostadil (injections or intraurethral suppository) and oral phosphodiesterase type 5 (PDE5) inhibitors.[8] Alprostadil may help the recovery of erectile function by promotion of cavernosal oxygenation levels.

A prospective study explored the idea of early intervention with injectable alprostadil to avoid cavernous hypoxia, tissue damage and subsequent ED in patients post-RP.[9] In this randomized study, patients (n = 30) either received alprostadil injections three times a week for 12 weeks, beginning 1 month post-RP or they were observed with no treatment to facilitate recovery of spontaneous erections. After 12 weeks, 67% of the patients that received alprostadil injections vs. 20% of the patients in the observation group reported recovery of spontaneous erections ($P < 0.01$). In another prospective study that assessed sexual rehabilitation post-RP with Edex, the Internation Index of Erectile Function (IIEF) score and Erection Hardness Score (EHS) increased significantly in patients (n = 87) between Month 6 and 12. After 12 months, the IIEF subscore was > 20 in 47% of patients using Edex compared with 2% of patients not using the injection.[10] A long-term efficacy and compliance study assessed the use of intracorporeal injections with alprostadil alone, in combination with high-dose phentolamine and papaverine (triple therapy) or low-dose triple therapy.[11] Patients were retrospectively stratified into the type of procedure they had: bilateral nerve sparing, unilateral nerve sparing, or non-nerve sparing. The study found that 68% of the patients that had intracavernous injections were satisfied with therapy and 48% of them chose to continue with therapy long-term (mean 3.5 years). Also, the type of prostatectomy surgery did not affect the efficacy of therapy. Another observational study noted that there was 94.6% success rate with the use of combination therapy with papaverine, phentolamine and prostaglandin E1 in patients (n = 168) where 40% had previously tried and failed oral therapy, MUSE, or vacuum device.[12]

Studies have also demonstrated the efficacy of MUSE for the treatment of ED post-RP. In a prospective study of patients (n = 91) post nerve-sparing RP, 56 patients were treated with MUSE (125 mcg or 250 mcg three times per week), while the remaining 35 patients had no treatment.[13] At the end of 9 months, 74% of the patients who remained on MUSE were able to have successful vaginal intercourse. In the observation group, 37% of patients reported some return of erectile function. MUSE was also found to provide good efficacy and compliance in up to 63% of patients in another long-term efficacy study.[14] MUSE was just as effective in patients that underwent non-nerve sparing RP as those who had nerve sparing RP procedures. A large, randomized, prospective, open-label trial also compared the effectiveness of daily MUSE therapy (125 mcg initially) vs. daily sildenafil citrate (50 mg) after nerve sparing prostatectomy.[7] The intercourse success rate for MUSE was 16% higher at 3 months and 41% higher at 6 months compared with sildenafil, but the differences were not statistically significant. Another study also showed that combination therapy with MUSE and sildenafil in patients who had previously tried and failed sildenafil therapy alone was effective in 83% of the patients.[15] Since each of these agents act through different mechanisms, they can augment each other and provide higher success rates in the treatment of ED post-RP.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of alprostadil injections and suppository administered via intracavernous or intraurethral routes, respectively. Intravenous (IV) or other routes of administration of alprostadil is not covered by this policy. All approvals are provided for 1 year in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of alprostadil injections (e.g., Edex, Caverject) and suppository (e.g., MUSE) is recommended in those who meet the following criteria:

Food and Drug Administration (FDA)-Approved Indications

1. **Men with Erectile Dysfunction (ED)**. Approve.

   Alprostadil injections and MUSE are indicated for the treatment of ED.[1-4]

Other Uses with Supportive Evidence

2. **Prophylaxis after Radical Prostatectomy (Early Penile Rehabilitation).** Approve in treatment-naïve men if they meet both of the following criteria (A and B).
   A) Therapy will be started within 6 months of surgery; AND
   B) Alprostadil (e.g., Edex, Caverject, MUSE) is prescribed by or in consultation with a urologist

   Several studies have demonstrated the efficacy of alprostadil injections and MUSE for early penile rehabilitation post radical prostatectomy.[9-15]

3. **Patient with a History of Radical Prostatectomy who is Continuing Alprostadil Therapy (e.g., Edex, Caverject, MUSE).** Approve if patient was started on therapy post-operatively and is currently continuing therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Alprostadil products (Caverject, Caverject Impulse, Edex, MUSE) have 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. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Pulmonary Arterial Hypertension (PAH).** There are very limited data available to support the use of alprostadil for the treatment of PAH. One published study used an IV formulation of PGE_1 (route of administration not covered by this policy)[16].

2. **Premature Ejaculation.** There are no data available to support the use of alprostadil for the treatment of premature ejaculation. Guidelines recommend the use of selective serotonin reuptake inhibitors (SSRIs) and topical anesthetics for the treatment of premature ejaculation.[17]

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date	Lay Criteria Effective Date
New Policy	--	10/31/2012	--
Annual revision	--	11/06/2013	--
Selected revision	Approval duration increased from 1 year to 3 years for ED. Approval duration remains 1 year for post-radical prostatectomy indication.	09/03/2014	09/19/2014
Annual revision	No criteria changes	11/05/2014	Previously in Effect
Annual revision	No criteria changes	11/11/2015	Previously in Effect
selected revision	Approval duration changed back to 1 year for all indications	12/02/2015	12/17/2015

TAC – Therapeutic Assessment Committee; * 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.