

MUSE[®]
(alprostadil) urethral
suppository



05-10-00001C

DESCRIPTION

MUSE[®] (alprostadil) is a single-use, medicated transurethral system for the delivery of alprostadil to the male urethra. Alprostadil is suspended in polyethylene glycol 1450 (as excipient) and is formed into a medicated pellet (micro-suppository measuring 1.4 mm in diameter by 3 mm or 6 mm in length) that resides in the tip of a translucent hollow applicator. MUSE is administered by inserting the applicator stem into the urethra after urination. The pellet containing alprostadil is delivered by depressing the applicator button (see Figure 1). The components of the delivery system are constructed of medical grade polypropylene. Each MUSE system is packaged in an individual foil pouch.

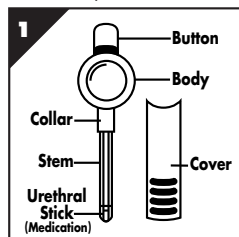
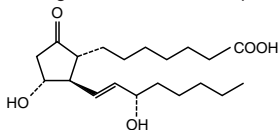


Figure 1: Diagram of the MUSE Transurethral System

The active ingredient in MUSE is alprostadil, which is chemically identical to the naturally occurring eicosanoid, prostaglandin E₁ (PGE₁). The chemical name for alprostadil is prost-13-en-1-oic acid, 11,15-dihydroxy-9-oxo-(11α,13E,15S)-(1R,2R,3R)-3-hydroxy-2-[(E)-(3S)-3-hydroxy-1-octenyl]-5-oxo-cyclopentane heptanoic acid, and the molecular weight is 354.49. The empirical formula is C₂₀H₃₄O₅. The



structural formula of alprostadil is represented below:

Alprostadil is a white to off-white crystalline powder with a melting point between 115° and 116°C. Its solubility at 35°C is 8000 mcg per 100 mL double-distilled water. The inactive ingredient in MUSE is polyethylene glycol 1450, USP. There are no other active agents or excipients in MUSE.

MUSE is available in 4 dosage strengths: 125 mcg, 250 mcg, 500 mcg, and 1000 mcg.

CLINICAL PHARMACOLOGY

Mechanism of Action: Prostaglandin E₁ is a naturally occurring acidic lipid that is synthesized from fatty acid precursors by most mammalian tissues and has a variety of pharmacologic effects. Human seminal fluid is a rich source of prostaglandins, including PGE₁ and PGE₂, and the total concentration of prostaglandins in ejaculate has been estimated to be approximately 100–200 mcg/mL. In vitro, alprostadil (PGE₁) has been shown to cause dose-dependent smooth muscle relaxation in isolated corpus cavernosum and corpus spongiosum preparations. Additionally, vasodilation has been demonstrated in isolated cavernosal artery segments that were pre-contracted with either norepinephrine or prostaglandin F_{2α}. When alprostadil was injected into the corpus cavernosum of pigtail monkeys in vivo, dose-dependent increases in cavernosal artery blood flow were observed.

In human studies using Doppler duplex ultrasonography, intraurethral administration of 500 mcg of MUSE resulted in an increase in cavernosal artery diameter and a 5- to 10-fold increase in peak systolic flow velocities. These results suggest that intraurethral alprostadil is absorbed from the urethra, transported throughout the erectile bodies by communicating vessels between the corpus spongiosum and corpora cavernosa, and able to induce vasodilation of the targeted vascular beds.

The vasodilatory effects of alprostadil on the cavernosal arteries and the trabecular smooth muscle of the corpora cavernosa result in rapid arterial inflow and expansion of the lacunar spaces within the corpora. As the expanded corporal sinusoids are compressed against the tunica albuginea, venous outflow through subintimal vessels is impeded and penile rigidity develops. This process is referred to as the corporal veno-occlusive mechanism.

The most notable systemic effects of alprostadil are vasodilation, inhibition of platelet aggregation, and stimulation of intestinal and uterine smooth muscle. Intravenous doses of 1 to 10 micrograms per kilogram of body weight lower blood pressure in mammals by decreasing peripheral resistance. Reflex increases in cardiac output and heart rate may accompany these effects.

Pharmacokinetics:

About 80% of alprostadil administered by MUSE is absorbed within 10 minutes and is rapidly cleared from the systemic circulation by the lungs, leaving barely detectable systemic blood levels.

Absorption: MUSE is designed to deliver alprostadil directly to the urethral lining for transfer via the corpus spongiosum to the corpora cavernosa. Intraurethral administration of MUSE is preceded by urination, and the residual urine disperses the medicated pellet, permitting alprostadil to be absorbed by the urethral mucosa. The transurethral absorption of alprostadil after MUSE administration is biphasic. Initial absorption is rapid, with approximately 80% of an administered dose absorbed within 10 minutes. The mean time to the maximum plasma PGE₁ concentration after a 1000 mcg intraurethral dose of MUSE is approximately 16 minutes.

In 10 normal human volunteers, endogenous PGE₁ levels in the ejaculate averaged 31 mcg (range 0–161 mcg). In these same volunteers, an average of 123 mcg of additional PGE₁ (range 30–369 mcg) was present in the ejaculate obtained 10 minutes after the highest dose (1000 mcg) of MUSE. The mean total endogenous PGE content (PGE₁, PGE₂, 19-OH-PGE₁, and 19-OH-PGE₂) of the ejaculate in these subjects was 444 mcg (range 0–1423 mcg).

Distribution: Following MUSE administration, alprostadil is absorbed from the urethral mucosa into the corpus spongiosum. A portion of the administered dose is transported to the corpora cavernosa through collateral vessels, while the remainder

passes into the pelvic venous circulation through veins draining the corpus spongiosum. The half-life of alprostadil in humans is short, varying between 30 seconds and 10 minutes, depending on the body compartment in which it is measured and the physiological status of the subject. Nearly all of the alprostadil entering the central venous circulation is removed in a single pass through the lungs; thus peripheral venous plasma levels of PGE₁ are low or undetectable (<2 picograms/mL) after MUSE administration. The mean maximum plasma PGE₁ concentration following intraurethral administration of the highest dose of MUSE (1000 mcg) was barely detectable (11.4 picograms/mL). In a study of 14 subjects, the plasma PGE₁ level was shown to be undetectable within 60 minutes of MUSE administration in most subjects.

Metabolism: Alprostadil is rapidly metabolized locally by enzymatic oxidation of the 15-hydroxyl group to 15-keto-PGE₁. The enzyme catalyzing this process has been isolated from many tissues in the lower genitourinary tract including the urethra, prostate, and corpus cavernosum. 15-keto-PGE₁ retains little (1–2%) of the biological activity of PGE₁. 15-keto-PGE₁ is rapidly reduced at the C₁₃-C₁₄ position to form the most abundant metabolite in plasma, 13,14-dihydro,15-keto PGE₁ (DHK-PGE₁), which is biologically inactive. The majority of DHK-PGE₁ is further metabolized to smaller prostaglandin remnants that are cleared primarily by the kidney and liver. Between 60% and 90% of PGE₁ has been shown to be metabolized after 1 pass through the pulmonary capillary beds.

Excretion: After intravenous administration of tritium-labeled alprostadil in man, labeled drug disappears rapidly from the blood in the first 10 minutes, and by 1 hour radioactivity in the blood reaches a low level. The metabolites of alprostadil are excreted primarily by the kidney, with approximately 90% of an administered intravenous dose excreted in the urine within 24 hours of dosing. The remainder is excreted in the feces. There is no evidence of tissue retention of alprostadil or its metabolites following intravenous administration.

Pharmacokinetics in Special Populations:

Pulmonary Disease: The near-complete pulmonary first-pass metabolism of PGE₁ is the primary factor influencing the systemic pharmacokinetics of MUSE and is a reason that peripheral venous plasma levels of PGE₁ are low or undetectable (<2 picograms/mL) following MUSE administration. Patients with pulmonary disease therefore may have a reduced capacity to clear the drug. In patients with the adult respiratory distress syndrome (ARDS), pulmonary extraction of intravascularly administered alprostadil was reduced by approximately 15% compared to a control group of patients with normal respiratory function (66±3.2% vs. 78±2.4%).

Geriatrics: The effects of age on the pharmacokinetics of alprostadil have not been evaluated.

CLINICAL TRIALS

The MUSE system was evaluated in 7 placebo-controlled trials of various design in over 2500 patients with a history of erectile dysfunction of various etiologies. These trials assessed erectile function in the clinic and sexual intercourse in outpatient settings. In studies of sexual performance, patients were screened in the clinic, generally using doses of 125 mcg to 1000 mcg, for a satisfactory erectile response, then sent home with the selected dose or placebo for evaluation of sexual performance. Not all patients beginning titration had a successful dose and some patients could not tolerate MUSE, principally because of penile pain, so that the success rates in the studies described below must be understood to represent response rates only in patients who were successfully titrated.

In 2 identical multicenter, double-blind, placebo-controlled, parallel-group studies, 1511 monogamous and heterosexual patients with a mean 4-year history of erectile dysfunction and at least a 3-month history of no erections adequate for sexual intercourse without medical assistance, were enrolled and began dose titration in the clinic with doses between 125 mcg and 1000 mcg. 996 patients (66%) completed dose titration, achieved an erection sufficient for intercourse, and were randomized equally to placebo or active treatment and followed during at-home treatment for up to 3 months. 874 patients and partners completed 3 months of follow-up. About 10%, 20%, 30%, and 40% of patients were titrated to 125 mcg, 250 mcg, 500 mcg, and 1000 mcg, respectively. Couples on active therapy were more likely to have at least 1 successful sexual intercourse (65% vs. 19%) than were couples on placebo. Among patients who reported successful intercourse at least once with active treatment, approximately 7 of 10 MUSE systems resulted in successful sexual intercourse. Results were similar in patients with erectile dysfunction stemming from surgery or trauma, diabetes, vascular disease, or other etiologies, and were similar in Caucasians and non-Caucasians. In administrations resulting in sexual intercourse, the duration of erections sufficient for penetration was 6 minutes on placebo and 16 minutes on active drug. Successful therapy with MUSE was associated with improvement in the quality of life measures of "emotional well-being" for patients and "relationship with partner" for both patients and their female partners.

INDICATIONS AND USAGE

MUSE 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.

CONTRAINDICATIONS

MUSE is contraindicated in men with any of the following:

1. Known hypersensitivity to alprostadil.
2. Abnormal penile anatomy: MUSE is contraindicated in patients with urethral stricture, balanitis (inflammation/infection of the glands of the penis), severe hypospadias and curvature, and in patients with acute or chronic urethritis.
3. Sickle cell anemia or trait, thrombocythemia, polycythemia, multiple myeloma: MUSE is contraindicated in patients who are prone to venous thrombosis or who have a hyperviscosity syndrome and are therefore at increased risk of priapism (rigid erection lasting 6 or more hours).
4. MUSE should not be used in men for whom sexual activity is inadvisable (see General Precautions).
5. MUSE should not be used for sexual intercourse with a pregnant woman unless the couple uses a condom barrier.

WARNINGS

Because of the potential for symptomatic hypotension and syncope, which occurred in 3% and 0.4%, respectively, of patients during in-clinic dosing, MUSE titration should be carried out under medical supervision. During post-marketing surveillance syncope occurring within one hour of administration has been reported. Patients should be cautioned to avoid activities, such as driving or hazardous tasks, where injury could result if hypotension or syncope were to occur after MUSE administration.

PRECAUTIONS**General Precautions:**

1. A complete medical history and physical examination should be undertaken to exclude reversible causes of erectile dysfunction prior to the initiation of MUSE therapy. In addition, underlying disorders that might preclude the use of MUSE

(see CONTRAINDICATIONS) should be sought.

- Cardiovascular effects:** During in-clinic dosing, patients should be monitored for symptoms of hypotension, and the lowest effective dose of MUSE should be prescribed.
- Hematologic effects:** Patients administering MUSE improperly may be at risk of urethral abrasion resulting in minor bleeding or spotting. Patients on anticoagulant therapy or with bleeding disorders may be at higher risk of bleeding. Patients on anticoagulant therapy have been safely treated with MUSE; however, the risk/benefit ratio in these patients should be considered prior to prescribing MUSE.
- Resumption of sexual activity:** Sexual intercourse is considered a vigorous physical activity, and it increases heart rate as well as cardiac work. Physicians may want to examine the cardiac fitness of patients prior to treating erectile dysfunction.
- Priapism and prolonged erection:** In clinical trials of MUSE, priapism (rigid erection lasting ≥ 6 hours) and prolonged erection (rigid erection lasting 4 hours and < 6 hours) were reported infrequently ($< 0.1\%$ and 0.3% of patients, respectively). Nevertheless, these events are a potential risk of pharmacologic therapy and can cause penile injury. Physicians should lower the dose or consider discontinuing MUSE treatment in any patient who develops priapism or prolonged erection.
- Drug-Drug Interactions:** Because there are low or undetectable (< 2 picograms/mL) amounts of alprostadil found in the peripheral venous circulation following MUSE administration, systemic drug-drug interactions with MUSE are unlikely. Although formal studies have not been conducted, the concomitant use of MUSE and anti-hypertensive medications may increase the risk of hypotension. It is therefore advised that caution be used in the administration of MUSE to individuals on anti-hypertensive medications. In addition, the presence of medications in the circulation that attenuate erectile function may influence the response to MUSE.
- Drug-Device Interactions:** Use of MUSE in patients with penile implants has not been studied.
- Sexual Preference:** There is no experience in homosexual men and no experience with other than vaginal intercourse.

Information for Patients:

Patients should be informed that MUSE offers no protection from the transmission of sexually transmitted diseases. Patients and partners who use MUSE need to be counseled about the protective measures that are necessary to guard against the spread of sexually transmitted agents, including the human immunodeficiency virus (HIV).

Although unreported in clinical trials, there is the possibility that an overdose of MUSE can cause priapism, a painful erection of the penis sustained for hours and unrelieved by sexual intercourse or masturbation. This condition is serious and, if untreated, it can lead to permanent inability to have an erection. Patients who experience a prolonged erection should seek prompt medical attention.

Patients should be instructed how to administer MUSE. A patient package insert must be given to each patient at the initiation of MUSE therapy.

Information for Partners:

Partners of patients using MUSE should be informed that MUSE offers no protection from the transmission of sexually transmitted diseases. Patients and partners who use MUSE should be counseled about the protective measures that are necessary to guard against the spread of sexually transmitted agents, including the human immunodeficiency virus (HIV). Human semen contains PGE₁, but additional amounts may be present from MUSE administration (see CLINICAL PHARMACOLOGY). Partners who have experienced an extended period of sexual abstinence should be encouraged to seek advice from a health care professional prior to resuming sexual intercourse. The use of a water-based lubricant may facilitate vaginal penetration.

It is recommended that couples using MUSE employ adequate contraception if the female partner is of childbearing potential. There is no information on the effects on early pregnancy of PGE₁ at the levels received by female partners. MUSE has no contraceptive properties. MUSE should not be used if the female partner is pregnant, unless the couple uses a condom barrier.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long-term carcinogenicity studies of alprostadil have not been conducted. Alprostadil showed no evidence of mutagenicity in vitro in the Ames bacterial reverse mutation test, the unscheduled DNA synthesis assay in rat hepatocytes, or the Chinese hamster ovary forward gene mutation assay; nor was there evidence of mutagenicity in vivo in the mouse micronucleus assay. Alprostadil concentrations increased chromosomal aberrations above control incidence in the in vitro Chinese hamster ovary chromosomal aberration assay.

In dogs, sperm concentration, morphology, and motility were unaffected by daily intraurethral administration of up to 3000 mcg MUSE (alprostadil) for 13 weeks (200 mcg/kg/day or about 3.5 times the maximum recommended daily dose adjusted for body surface area). Alprostadil concentrations of 400 mcg/mL had no effect on human sperm motility or viability in vitro.

Pregnancy: Pregnancy Category C: Alprostadil has been shown to be embryotoxic (decreased fetal weight) when administered as a subcutaneous bolus to pregnant rats at doses as low as 500 mcg/kg/day. Doses of 2000 mcg/kg/day resulted in increased resorptions, reduced numbers of live fetuses, increased incidences of visceral and skeletal variations (primarily left umbilical artery and generalized reduction in ossification of the entire skeleton) and gross visceral and skeletal malformations (primarily edema, hydrocephaly, anophthalmia/microphthalmia, and skeletal anomalies). The latter dose produced maternal toxicity (ataxia, lethargy, diarrhea, and retarded body weight gain). When administered by continuous intravenous infusion, evidence of embryotoxicity (decreased fetal weight gain and increased incidence of hydronephrosis) was observed at 2000 mcg/kg/day, a dose that was also associated with a decrease in maternal weight gain. Intravaginal administration of up to 4000 mcg/day of MUSE (alprostadil) to pregnant rabbits (1100 mcg/kg/day or about 12.5 times the maximum recommended daily dose adjusted for body surface area) resulted in no evidence of harm to the fetus. MUSE should not be used for sexual intercourse with a pregnant woman unless the couple uses a condom barrier.

Nursing Mothers and Pediatric Use:

MUSE is not indicated for use in newborns, children, or women.

ADVERSE REACTIONS

In-Clinic Titration:

In the 2 largest double-blind, parallel, placebo-controlled trials, 1511 patients received MUSE at least 1 time in the clinic setting. The most frequently reported drug-related side effects during in-clinic titration included pain in the penis (36%), urethra (13%), or testes (5%). These discomforts were most commonly reported as mild and transient, but about 7% of patients withdrew at this stage because of adverse events. Urethral bleeding/spotting and other minor abrasions to the urethra were reported in approximately 3% of patients. Symptomatic lowering of blood pressure (hypotension) occurred in 3% of patients; in addition, some lowering of blood pressure may occur without symptoms. Dizziness was reported in 4% of patients. Syncope (fainting) was reported

by 0.4% of patients. (See **WARNINGS**).

Home Treatment:

996 patients (66% of those who began titration) were studied during the home treatment portion of 2 Phase III placebo-controlled studies. Fewer than 2% of patients discontinued from these studies primarily because of adverse events. The following table summarizes the frequency of adverse events reported by patients using MUSE or placebo.

Adverse Events Reported by $\geq 2\%$ of Patients Treated with MUSE, and More Common than on Placebo, at Home in Phase III Placebo-Controlled Clinical Studies for up to 3 Months

Event	MUSE n = 486	Placebo n = 511	Event	MUSE n = 486	Placebo n = 511
UROGENITAL SYSTEM			BODY AS A WHOLE		
Penile Pain	32%	3%	Flu Symptoms	4%	2%
Urethral Burning	12%	4%	Headache	3%	2%
Minor Urethral Bleeding/ Spotting	5%	1%	Pain	3%	1%
Testicular Pain	5%	1%	Accidental Injury	3%	2%
NERVOUS SYSTEM			Back Pain	2%	1%
Dizziness	2%	<1%	Pelvic Pain	2%	<1%
			RESPIRATORY		
			Rhinitis	2%	<1%
			Infection	3%	2%

Other drug-related side effects observed during in-clinic titration and home treatment include swelling of leg veins, leg pain, perineal pain, and rapid pulse, each occurring in $< 2\%$ of patients.

Female Partner Adverse Events: The most common drug-related adverse event reported by female partners during placebo-controlled clinical studies was vaginal burning/itching, reported by 5.8% of partners of patients on active vs. 0.8% of partners of patients on placebo. It is unknown whether this adverse event experienced by female partners was a result of the medication or a result of resuming sexual intercourse, which occurred much more frequently in partners of patients on active medication.

To report suspected adverse reactions, contact Meda Pharmaceuticals Inc. at 1-888-345-6873 or contact FDA at 1-800-FDA-1088, fax 1-800-FDA-0178 or online at www.fda.gov/medwatch/report.htm.

OVERDOSAGE

Overdosage has not been reported with MUSE. Overdosage with MUSE may result in hypotension, persistent penile pain, and possibly priapism (rigid erection lasting ≥ 6 h). Priapism can result in permanent worsening of erectile function. Patients suspected of overdosage who develop these symptoms should be kept under medical supervision until systemic or local symptoms have resolved.

DOSAGE AND ADMINISTRATION

MUSE is a transurethral delivery system available in 4 dosage strengths: 125 mcg, 250 mcg, 500 mcg, and 1000 mcg. MUSE should be administered as needed to achieve an erection. The onset of effect is within 5–10 minutes after administration. The duration of effect is approximately 30–60 minutes. However, the actual duration will vary from patient to patient. Each patient should be instructed by a medical professional on proper technique for administering MUSE prior to self-administration. The maximum frequency of use is no more than 2 systems per 24-hour period.

Initiation of Therapy:

Dose titration should be administered under the supervision of a physician to test a patient's responsiveness to MUSE, to demonstrate proper administration technique (see detailed instructions for MUSE administration in patient package insert), and to monitor for evidence of hypotension (see **WARNINGS**). Patients should be individually titrated to the lowest dose that is sufficient for sexual intercourse. The lower doses of MUSE (125 mcg or 250 mcg) are recommended for initial dosing. If necessary, the dose should be increased (or decreased) on separate occasions in a step-wise manner until the patient achieves an erection that is sufficient for sexual intercourse.

Home Treatment Regimen:

MUSE should be used as needed to achieve an erection. The maximum frequency of use is 2 administrations per 24-hour period. Each MUSE is for single use only and should be properly discarded after use.

HOW SUPPLIED

MUSE is supplied in individual foil pouches containing one (1) system per pouch. MUSE is available in unit cartons containing six (6) systems. MUSE is available in the following 4 dosage strengths:

Dosage Strength	NDC Numbers		Identifying Package Color
	Carton	Pouch	
125 mcg	0037-8110-06	0037-8110-01	Tan
250 mcg	0037-8120-06	0037-8120-01	Green
500 mcg	0037-8130-06	0037-8130-01	Blue
1000 mcg	0037-8140-06	0037-8140-01	Burgundy

 Only.

STORAGE AND HANDLING

Store unopened foil pouches in a refrigerator at 2°– 8°C (36°– 46°F). Do not expose MUSE to temperatures above 30°C (86°F). MUSE may be kept by the patient at room temperature (below 30°C or 86°F) for up to 14 days prior to use.

Medical information line at Meda Pharmaceuticals Inc. 1-888-345-MUSE (1-888-345-6873).

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