

PRODUCT MONOGRAPH

PrMUSE*
(Alprostadil)

125 mcg, 250mcg, 500mcg, 1000mcg Micro-Suppositories

Prostaglandin

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Control No.: 130077

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PRODUCT MONOGRAPH

PrMUSE*

alprostadil micro-suppository

Prostaglandin

CLINICAL PHARMACOLOGY

Actions

Alprostadil is a synthetic prostaglandin with various pharmacological actions that include vasodilation, inhibition of platelet aggregation, inhibition of gastric secretion, stimulation of intestinal smooth muscle and stimulation of uterine smooth muscle.

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 $\mu\text{g/mL}$.

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 subtunical vessels is impeded and penile rigidity develops. This process is referred to as the corporal veno-occlusive mechanism.

Pharmacokinetics

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

Absorption

MUSE alprostadil is designed to deliver alprostadil directly to the urethral lining for transfer via the corpus spongiosum to the corpora cavernosa. Intraurethral administration of MUSE alprostadil 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 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 µg intraurethral dose of MUSE alprostadil is approximately 16 minutes.

Distribution

Following administration, MUSE 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 alprostadil (1000 μg) 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 alprostadil 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 one pass through the pulmonary capillary beds. However, pulmonary clearance of PGE₁ can be affected by disease states such as acute respiratory distress syndrome (ARDS), with a resultant reduction in the pulmonary extraction ratio.

Excretion

After intravenous administration of tritium-labelled alprostadil in man, labelled 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 alprostadil and is a reason that peripheral venous plasma levels of PGE₁ are low or undetectable (<2 picograms/mL) following 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 Experience

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.

Studies that established benefit demonstrated improvements in success rates for sexual intercourse compared with similarly administered placebo.

In 2 identical multicentre, double-blind, placebo-controlled, parallel-group studies, 1511 monogamous and heterosexual patients were enrolled and began dose titration in the clinic with doses between 125 μg and 1000 μg . Sixty-six percent of patients (996) completed dose titration and achieved an erection sufficient for intercourse. Couples on active therapy were more likely to have at least one 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. In administrations resulting in sexual intercourse,

average erections sufficient for penetration was 16 minutes on active drug. Successful therapy with MUSE alprostadil 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 CLINICAL USE

MUSE alprostadil is indicated for the treatment of erectile dysfunction. MUSE alprostadil may also be useful as an adjunct to diagnostic tests in the diagnosis of erectile dysfunction.

CONTRAINDICATIONS

MUSE alprostadil is contraindicated in men with any of the following:

1. Known hypersensitivity to alprostadil.
2. Abnormal penile anatomy: MUSE alprostadil is contraindicated in patients with urethral stricture, balanitis (inflammation/infection of the glans of the penis), severe hypospadias and curvatures, and in patients with acute or chronic urethritis.
3. Sickle cell anemia or trait, thrombocythemia, polycythemia, multiple myeloma: MUSE alprostadil 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 alprostadil should not be used in men for whom sexual activity is inadvisable (see PRECAUTIONS - General)

5. MUSE alprostadil 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.

There exists a possibility of syncope or fainting occurring within one hour of post-administration of MUSE alprostadil. 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 the administration of MUSE alprostadil.

PRECAUTIONS

General

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

2. Cardiovascular effects: During in-clinic dosing, patients should be monitored for symptoms of hypotension, and the lowest effective dose of MUSE alprostadil should be prescribed.

3. Hematologic effects: Patients administering MUSE alprostadil 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 alprostadil; however, the risk/benefit ratio in these patients should be considered prior to prescribing MUSE alprostadil.

4. 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.

5. Priapism and prolonged erection: In clinical trials of MUSE alprostadil, 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 treatment with MUSE alprostadil in any patient who develops priapism or prolonged erection.

6. Drug-Drug Interactions: Because there are low or undetectable (<2 picograms/mL) amounts of alprostadil found in the peripheral venous circulation following administration, systemic drug-drug interactions with MUSE alprostadil are unlikely. The presence of medications in the circulation that attenuate erectile function, however, may influence the response to MUSE alprostadil.

Although formal studies have not been conducted, the concomitant use of MUSE alprostadil and anti-hypertension medications may increase the risk of hypotension. It is therefore advised that caution be used in the administration of MUSE alprostadil to individuals on anti-hypertensive medications. In addition, the presence of medication in the circulation that attenuate erectile function may influence the response to MUSE alprostadil.

7. Drug-Device Interactions: Use of the MUSE system in patients with penile implants has not been studied.
8. Sexual Preference: There is no experience in homosexual men and no experience with other than vaginal intercourse.

Nursing Women and Pediatric Use

MUSE alprostadil is not indicated for use in women or children.

ADVERSE REACTIONS

In-Clinic Titration

In the 2 largest double-blind, parallel, placebo-controlled trials, 1511 patients received MUSE alprostadil 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. Dizziness was reported in 4% of patients. Syncope (fainting) was reported by 0.4% of patients.

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 alprostadil or placebo.

Adverse Events Reported by $\geq 2\%$ of Patients Treated with MUSE alprostadil 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 |
|----------------------------------|-----------------|--------------------|
| UROGENITAL SYSTEM | | |
| Penile Pain | 32% | 3% |
| Urethral Burning | 12% | 4% |
| Minor Urethral Bleeding/Spotting | 5% | 1% |
| Testicular Pain | 5% | 1% |
| NERVOUS SYSTEM | | |
| Dizziness | 2% | <1% |
| BODY AS A WHOLE | | |
| Flu symptoms | 4% | 2% |
| Headache | 3% | 2% |
| Pain | 3% | 1% |
| Accidental Injury | 3% | 2% |
| Back Pain | 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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage has not been reported with MUSE alprostadil. Overdosage with MUSE alprostadil 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 and/or until penile detumescence has occurred. Symptomatic treatment of any systemic symptoms would be appropriate.

Patients should be instructed to report any erections persisting for more than 4 hours to a physician. The treatment of priapism/prolonged erection should be according to established medical practice. Physicians may refer to two suggested protocols for detumescence presented below.

Detumescence Protocols

1. Aspirate 40 to 60 mL from either right or left corpora using vacutainer and holder as for drawing blood. Patient will often detumescence while aspirating. Apply ice for 20 minutes post aspiration if erection remains.

If 1) unsuccessful then,

2. Have patient in supine position. Dilute 10 mg phenylephrine into 20 mL water for injection (0.05%). With an insulin syringe, inject 0.1 to 0.2 mL (50-100) μg into the corpora every 2 to 5 minutes, until detumescence occurs. The occasional patient may experience very transient bradycardia and hypertension when given phenylephrine injections, therefore

monitor patient's blood pressure and pulse every 10 minutes. Patients at risk include those with cardiac arrhythmias and diabetics. Refer to the prescribing information for phenylephrine before use. DO NOT give to patients on MAO inhibitors. When phenylephrine is used within the first 12 hours of erection, the majority of patients will respond.

3. If the above measures fail to detumescence the patient, a urologist should be consulted as soon as possible, especially if the erection has been present for many hours. If priapism is not treated immediately, penile tissue damage and/or permanent loss of potency may result.

DOSAGE AND ADMINISTRATION

MUSE alprostadil is a transurethral delivery system available in 4 dosage strengths: 125 μg , 250 μg , 500 μg and 1000 μg . MUSE alprostadil 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 alprostadil 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 undertaken under the supervision of a physician to test a patient's responsiveness to MUSE alprostadil, to demonstrate proper administration technique (see

detailed instructions for the administration of MUSE alprostadil in the patient package insert), and to monitor for evidence of hypotension. Patients should be individually titrated to the lowest dose that is sufficient for sexual intercourse. The lower dose of MUSE alprostadil (250 μg) is recommended for initial dosing. If necessary, the dose should be increased on separate occasions in a stepwise manner until the patient achieves an erection that is sufficient for sexual intercourse.

Home Treatment Regimen

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

PHARMACEUTICAL INFORMATION

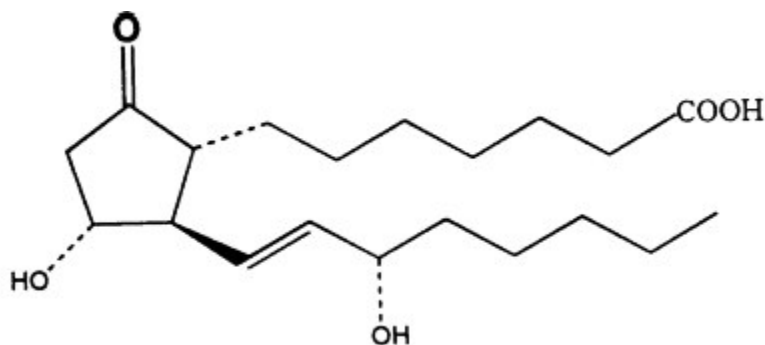
Drug Substance

Trade Name: MUSE

Proper Name: alprostadil

Chemical Name: prost-13-en-1-oic acid, 11,15-dihydroxy-
9-oxo-(11 α ,13E,15S)-(1R,2R,3R)-
3-hydroxy-2-[(E)-(3S)-3-hydroxy-1-
octenyl]-5-oxo-cyclopentane heptanoic acid

Structural Formula:



Molecular Formula: $C_{20}H_{34}O_5$

Molecular Weight: 354.49

Description: 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 μg per 100 mL double-distilled water.

Composition: The inactive ingredient in MUSE alprostadil is polyethylene glycol 1450, USP. There are no other active agents or excipients in the MUSE system.

STABILITY AND STORAGE RECOMMENDATIONS

Store unopened foil pouches in a refrigerator at 2°- 8°C. Do not expose MUSE alprostadil to temperatures above 30°C. The MUSE system may be kept by the patient at room temperature (below 30°C) for up to 14 days prior to use.

AVAILABILITY OF DOSAGE FORMS

MUSE alprostadil is a transurethral delivery system available in 4 dosage strengths: 125 μ g, 250 μ g, 500 μ g and 1000 μ g.

INFORMATION FOR THE PATIENT

Please read this pamphlet before using the MUSE system. This pamphlet is a quick reference source of important information about the MUSE system for you and your partner.

What is the MUSE system?

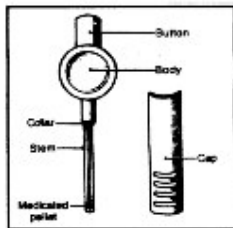


Fig. 1

The MUSE system represents a unique approach for the treatment of erectile dysfunction, commonly called impotence. It is based on the discovery that the urethra (the normal pathway for urine) can absorb certain medications into the surrounding erectile tissues thereby creating an erection. There are 4 dose strengths available: 125, 250, 500 and 1000 micrograms. The MUSE applicator (Fig.1) contained in each foil pouch is intended for 1 administration only. Your dose will be determined by you and your physician. After administration, the erection process will begin within 5 - 10 minutes, and may last 30 - 60 minutes. However, the actual duration will vary from patient to patient.

What is the MUSE system used for?

The MUSE system is indicated for the treatment of erectile dysfunction. Erectile dysfunction is the inability to attain or maintain an erection sufficient for sexual intercourse.

Who should not use the MUSE system?

You should not use the MUSE system if you have any of the following:

- Known hypersensitivity to alprostadil (the active medication in a MUSE micro-suppository)
- An abnormally formed penis
- Have been advised not to undertake sexual activity
- Conditions that might result in long-lasting erections, such as sickle cell anemia or trait, leukemia, or tumour of the bone marrow (multiple myeloma)
- The MUSE system should not be used for sexual intercourse with a pregnant woman unless the couple uses a condom barrier.

What Are the Possible Side Effects of a MUSE micro-suppository?

The most common side effects that have been observed using a MUSE micro-suppository are as follows:

- Aching in the penis, testicles, legs, and in the perineum (area between the penis and rectum)
- Warmth or burning sensation in the urethra
- Redness of the penis due to increased blood flow
- Minor urethral bleeding or spotting due to improper administration.

Side effects reported less frequently:

- Prolonged erection - PLEASE NOTE: IF YOUR ERECTION IS RIGID FOR MORE THAN 4 HOURS,

CALL YOUR DOCTOR PROMPTLY.

- Fainting - Please note: After using the MUSE system, you should avoid activities, such as driving or hazardous tasks, where injury could result if dizziness or fainting were to occur. In patients experiencing these symptoms, the symptoms have usually occurred during initiation of therapy and within one hour of MUSE administration.
- Swelling of leg veins
- Light-headedness/Dizziness
- Fainting
- Rapid pulse.

If you have a history of fainting be sure to discuss this with your doctor prior to using the MUSE system. If you do experience dizziness or feel faint, this may be due to the lowering of your blood pressure. Lie down immediately and raise your legs. If symptoms persist, call your doctor promptly. Because of the potential for these side effects, MUSE titration should be carried out under medical supervision.

Changing your Dosage

It is assumed that you and your doctor have determined the proper dose. If you suspect that your dose needs to be increased or decreased to achieve the response that works best for you, please call your doctor to determine if your dose needs to be reevaluated. **Do not use more than two MUSE systems in a 24-hour period.**

WHAT ARE THE POSSIBLE SIDE EFFECTS OF THE MUSE SYSTEM FOR YOUR PARTNER?

The most common reported side effects observed in women whose partners use the MUSE system are mild vaginal itching or burning. Using a water-based lubricant can help to make vaginal penetration easier. Your partner may want to consult her health care provider if she has not had sexual intercourse for an extended period of time.

Important Information for You and Your Partner

Pregnancy

A MUSE micro-suppository has no contraceptive properties.

Because the MUSE system has not been tested during human pregnancy, it is recommended that couples use adequate contraception if the female partner is of childbearing potential. The MUSE system should not be used for sexual intercourse with a pregnant woman unless the couple uses a condom barrier.

Sexually Transmitted Diseases

The MUSE system will not protect you or your partner from sexually transmitted diseases like chlamydia, gonorrhea, herpes simplex virus, viral hepatitis, human immunodeficiency virus (HIV- the virus that causes AIDS), human papilloma virus (genital warts), and syphilis. Latex condoms can protect against these sexually transmitted diseases.

How Should I Store the MUSE system?

It is recommended that the MUSE system be stored in a refrigerator. The MUSE system may be kept at room temperature (less than 30°C) for up to 14 days prior to use. It is very important that MUSE micro-suppositories not be exposed to temperatures above 30°C since this will make it ineffective. The MUSE system should not be exposed to high temperatures or placed in direct sunlight.

Storage when Travelling

When travelling, store MUSE systems in a portable ice pack or cooler. Do not store in the trunk of a car or in baggage storage areas where the MUSE system may be exposed to extremes in temperature.

How to Administer a MUSE micro-suppository:

1. Immediately prior to administration, urinate and gently shake the penis several times to remove excess urine. A moist urethra makes administration of the MUSE system easier. The medicated pellet has been specially developed to dissolve in the small quantity of urine that remains in the urethra after urination.
2. Open the foil pouch by tearing fully across from the notched edge (Fig. 2). Let the MUSE applicator slide out of the pouch. Save the pouch for discarding the MUSE applicator later.

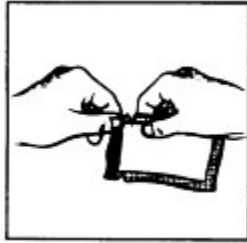


Fig. 2

3. To remove the protective cap from the applicator stem (Fig. 3), hold the body of the applicator with your thumb and forefinger. Twist the body and pull out the applicator from the cap, being careful not to push the applicator button. Avoid touching the applicator stem and tip. Save the cap for discarding the MUSE applicator later.



Fig. 3

4. Visually inspect the MUSE applicator. The MUSE system is see-through, and you will be able to see the medicated pellet at the end of the stem. Make sure that the pellet is present before insertion.

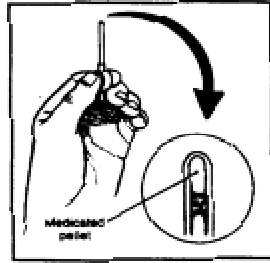


Fig.4

5. Hold the applicator in a way which is the most comfortable for you (Fig. 5A and 5B).

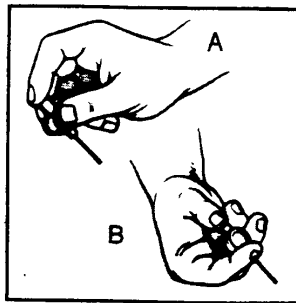


Fig. 5

6. Please review Figure 6A, the anatomy of the penis.

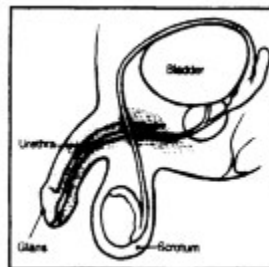


Fig. 6A

While sitting or standing, whichever is more comfortable for you, take several seconds to gently and slowly stretch the penis upward to its full length, with gentle compression from top to bottom of the glans (Fig. 6B). This straightens and opens the urethra. Slowly insert the MUSE stem into the urethra up to the collar (Fig. 6C). If you feel any discomfort or a pulling sensation, withdraw the applicator slightly and then gently reinsert.

Fig. 6B



Fig. 6C



7. Gently and completely push down (Fig. 7) the button at the top of the applicator until it stops. It is important to do this to ensure that the medicated pellet is completely released. Hold the applicator in this position for 5 seconds.

Fig. 7



8. Gently rock the applicator from side to side. This will separate the medicated pellet from the applicator tip (Fig. 8). If you apply too much pressure you may scratch the lining of the urethra causing it to bleed.

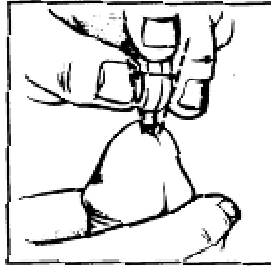


Fig. 8

9. Remove the applicator while keeping the penis upright.
10. Visually inspect the applicator tip to see that the medication is no longer in the applicator. Do not touch the stem. If you notice some residual medication in the end of the applicator, gently reinsert into the urethra and repeat steps 7, 8, and 9.
11. Holding the penis upright and stretched to its full length, roll the penis firmly between your hands for at least 10 seconds. This will ensure that the medication is adequately distributed along the walls of the urethra (Fig. 9). If you feel a burning sensation, it may help to continue to roll the penis for an additional 30 - 60 seconds or until the burning subsides.

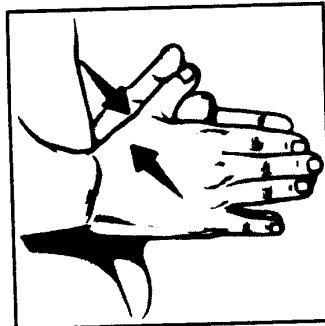


Fig. 9

12. Remember, each MUSE system is good for a single administration only. Replace the cap on the MUSE applicator, place in the opened foil pouch, fold, and discard as normal household waste.

After you have administered the MUSE system, it is important to sit, stand or walk about for 10 minutes while the erection is developing. This increases blood flow to the penis and will enhance your erection.

Additional Information and Practical Tips

Factors Which May Enhance Your Erection:

- Being well rested and relaxed
- Sexual foreplay with your partner or self-stimulation while sitting or standing
- Pelvic exercises (for example, Kegel exercises) - these consist of tightening and releasing your pelvic and buttock muscles. These are the muscles you use to stop urination
- Various positions that may favour blood flow into the penis.

Factors Which May Reduce Your Erection:

- Incorrect administration
- Anxiety, fatigue, tension, and too much alcohol
- Lying on your back too soon after administration of a MUSE micro-suppository may decrease blood flow to the penis and result in loss of erection
- Urination or dribbling immediately following administration may result in loss of medication from the urethra

- Using medications that contain decongestants, such as over-the-counter cold remedies, allergy, sinus medications, and appetite suppressants, may block the effect of the MUSE micro-suppository.

Commonly Asked Questions About the MUSE system

Will insertion of the MUSE applicator hurt?

At first, you may feel some minor discomfort from insertion. Urinating prior to administration will reduce the chance of discomfort or abrasions and is important for dissolving the medicated pellet. Be sure to straighten your penis to its full length when inserting the MUSE applicator. With repeated use, administration will become much easier.

What are the side effects associated with the MUSE system?

Most of the side effects reported in men are relatively minor and include burning and aching in the penis and groin. Rarely noted are prolonged erection, light-headedness, dizziness, fainting, rapid pulse, and swelling of the leg veins. If you feel dizzy, light-headed, faint, or experience rapid pulse, lie down immediately and raise your legs. If symptoms persist, call your doctor promptly. Because of the potential for these side effects, MUSE titration should be carried out under medical supervision. In women, mild vaginal itching and burning have been observed.

After I administer a MUSE micro-suppository, can we immediately lie down and begin sexual activity? You can begin sexual activity, but having the man lie down, especially on his back shortly after administration, is not recommended. This will reduce blood flow to the penis and may reduce the erection. It is important to sit, stand or walk about for 10 minutes after administration. Many

couples have used this time to incorporate various types of foreplay. After this initial period, you can assume different positions leading to sexual intercourse. Some couples have noticed that the erection is better maintained in positions that favour blood flow into the penis during intercourse.

How long will the effect of a MUSE system last?

An erection should begin within 5 - 10 minutes after administering a MUSE micro-suppository. The duration of effect is approximately 30 - 60 minutes. However, the actual duration will vary from patient to patient.

What will the erection be like? How will it compare to the erections I had when I was younger?

An effective dose of alprostadil should produce an erection sufficient for sexual intercourse. The alprostadil in the MUSE system may not create an erection such as those you experienced when you were younger. Some patients may experience some mild pain and aching in the penis or groin area. Also, your erection may continue after orgasm.

How do I know if I have the correct dose?

You and your physician will determine the appropriate dose. If your erection cannot be maintained for the time needed to have foreplay and sexual intercourse, you may need to have your dose increased. Similarly, an erection that lasts longer than desired may require a dose decrease. Call your doctor if you suspect you may require a dosing adjustment.

After my erection is over, will my penis feel sensitive?

Your penis may feel full, warm, and somewhat sensitive to the touch. These effects are normal and may last a few hours.

Can I reuse the MUSE system?

No. The MUSE system is intended for single-dose application only.

How do I dispose of the MUSE applicator?

After you have administered a MUSE micro-suppository, replace the cap on the applicator, place in the opened foil pouch, fold, and discard as normal household waste.

If my erection lasts longer than desired, what should I do?

Note: Call your doctor promptly if you have a rigid erection that lasts more than 4 hours.

An application of ice packs to the inner thigh may shorten the duration of the erection, since the cold will restrict blood flow to the penis. If used, ice packs should be applied alternately to each inner thigh for a period not exceeding 10 minutes.

How often can I safely use a MUSE system?

A MUSE system should not be used more than twice per day.

If you have any additional questions about the MUSE system, please call us toll free at 1-888-376-7830.

PHARMACOLOGY

Human

Pharmacodynamics

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}.

In human studies using Doppler duplex ultrasonography, intraurethral administration of 500 μg of MUSE alprostadil 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 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.

Human

Pharmacokinetics

Alprostadil is well absorbed (greater than 80%) following intraurethral administration. Following absorption alprostadil enters the venous blood system and is transported to the pulmonary circulation. First-pass metabolism through the lungs is substantial leading to low systemic plasma concentrations of PGE₁. While intraurethrally administered alprostadil requires a greater dose for activity than does intracavernosally administered alprostadil, it does not appear to pose a greater risk for systemic exposure because of efficient pelvic and pulmonary pre-systemic metabolism of alprostadil.

Absorption

Information from pharmacokinetic studies gives significant information on the absorption profile of alprostadil following the administration of MUSE alprostadil. The percentage of the dose remaining to be absorbed (PRA) indicated that approximately 80% of the intraurethrally administered dose was absorbed within 10 minutes. These PRA estimates were used to estimate the first-order absorption rate constant (K_a) of alprostadil from the urethra. The estimate of K_a was 0.285 min⁻¹. This estimate was determined by naive pooling of the data and served primarily to indicate that the absorption of alprostadil from the urethra is very rapid. A separate study assessing the mean contributions to PGE₁ in the semen (123 μg at 10 minutes and 110 μg at 30 minutes) indicated that 12.3% and 11.0% of the administered dose remains unabsorbed at 10 and 30 minutes after administration respectively. At least 87% of the administered dose has been absorbed from the urethra by 10 minutes after the administration of MUSE alprostadil. However, this does not reflect the systemic bioavailability due to significant first-pass extraction of PGE₁.

Distribution

Alprostadil is extensively metabolized on a single pass through the lungs, limiting the amount of alprostadil which may pass on to the systemic circulation. Cox et al [1988] reported the normal extraction efficiency to be 70% to 90% on a single pass through the lungs. Pulmonary clearance of PGE₁, cardiac output, and PGE₁ input rate are the primary factors controlling the plasma concentration of PGE₁.

Mean PGE₁ C_{max} observations in pharmacokinetic studies with MUSE alprostadil, following intravenous infusion and 1000 µg intraurethral administration, were 6.55 and 11.41 pg/mL, respectively. These concentrations are consistent with the literature reports of extensive first-pass metabolism of alprostadil, which will limit systemic exposure.

Metabolism

In pharmacokinetic studies, the bioavailability of PGE₁ following 1000 µg MUSE administration relative to intravenous infusion was estimated to be 7% in one subject based on plasma PGE₁ concentrations. The mean estimate of the bioavailability of PGE₁ based on the 13,14-dihydro-15-keto-PGE₁ metabolite was 23%. This low extent of bioavailability indicates there may be substantial first-pass metabolism of PGE₁ in the genitourinary tract following absorption. Substantial 15-hydroxyprostaglandin dehydrogenase activity has been measured in the tissues of the lower genitourinary tract, including the urethra. This is the major enzyme responsible for oxidation of the 15-hydroxyl group into a 15-keto moiety which starts the pathway of PGE₁ metabolic inactivation.

Following absorption, PGE₁ is rapidly metabolized in the lungs. A major pathway of PGE₁ metabolism is enzymatic oxidation of the 15-hydroxy-group, with subsequent reduction of the Δ^{13} double-bond to form 13,14-dihydro-15-keto-PGE₁. 13,14-dihydro-15-keto-PGE₁ is a major circulating metabolite of PGE₁ following IV and intraurethral administration.

Excretion

Removal of PGE₁ from the body is primarily through metabolism, with 88% of the metabolites excreted in the urine, and the remainder excreted in the feces. There is no evidence of alprostadil or its metabolites being retained in the tissues following intravenous administration.

TOXICOLOGY

Acute Toxicity

No non-clinical single-dose or acute toxicity studies of alprostadil were found in the literature.

Long-term Toxicity

The long-term toxicity of MUSE alprostadil was assessed in several non-clinical toxicity studies in rabbits and dogs. MUSE alprostadil was considered non-toxic and was well-tolerated when administered into the penile urethra with doses of up to 3000 μ g. Dose related clinical signs of penile erythema, enlargement and firmness are not considered adverse and are consistent with the known pharmacologic effects of alprostadil.

Impairment of Fertility

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

Carcinogenesis

Long-term carcinogenicity studies of alprostadil have not been conducted.

Mutagenicity

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.

BIBLIOGRAPHY

Non-Clinical

1. Cassin S, Tyler T, Wallis R. The effects of prostaglandin E₁ on fetal pulmonary vascular resistance. *Proc Soc Exp Biol Med.* 1975; 148(2):584-7.
2. Hamberg M, Israelsson U, Samuelsson B. Metabolism of prostaglandin E₂ in guinea pig liver. *Ann NY Acad Sci* 1971; 180:164-80.
3. Marks TA, Morris DF, Weeks JR. Developmental toxicity of alprostadil in rats after subcutaneous administration or intravenous infusion. *Toxicol Appl Pharmacol.* 1987; 91:341-57.
4. Moncada S, Gryglewski R, Bunting S, Vane DR. An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. *Nature.* 1976; 263:663-5.
5. Owen JS. Relevant Pharmacokinetics of Alprostadil (PGE₁) Following Intraurethral Administration of MUSE Alprostadil to Male Dogs. Final Report May, 1996.
6. Rao KS, Reno FE. Subacute toxicity studies with prostaglandin E₁ (PGE₁) in laboratory animal species. *J Toxicol Environ Health.* 1976; 1:495-504.
7. Ryan MJ, Clark KE, Van Orden DE, Farley D, Edvinsson L, Sjoberg NO, Van Orden LS, Brody MJ. Role of prostaglandins in estrogen-induced uterine hyperemia. *Prostaglandins.* 1974; 5(3):257-68.
8. Samuelsson B. Synthesis of tritium-labelled prostaglandin E₁ and studies on its distribution and excretion in the rat. *J Biol Chem.* 1964; 239:4091-96.
9. Stackl W, Loupal G, Holtzmann A. Intracavernous injections of vasoactive drugs in the rabbit. *Urol Res.* 1988; 16:455-8.

BIBLIOGRAPHY

Clinical

1. Buffum J. Prescription drugs and sexual function. *Psychiatry Med.* 1992; 10:181-198.
2. Feldman HA, Goldstein I, Hatzichristou DG, et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol.* 1994; 151:54-61.
3. Hamberg M, Samuelsson B. On the metabolism of prostaglandins E₁ and E₂ in man. *J Biol Chem.* 1971; 246(22):6713-21.
4. Hellstrom WJG, Bennett AH, Gesundheit N, et al. A Double-Blind, Placebo-Controlled Evaluation of The Erective Response to Transurethral Alprostadil*. *Urology.* 1996; 48:851-856.
5. Krane RJ, Goldstein I, Saenz de Tejada I. Impotence. *N Engl J Med.* 1989; 321:1648-1659.
6. Linet OI, Neff LL. Intercavernous prostaglandin E₁ in erectile dysfunction. *Clin Investig.* 1994; 72:139-149.
7. Linet OI, Ogrinc FG, Alprostadil Study Group. Efficacy and safety of intracavernosal alprostadil in men with erectile dysfunction. *N Engl J Med.* 1996; 334:873-877.
8. Lue TF. Impotence after radical pelvic surgery: physiology and management. *Urol Int.* 1991; 46:259-265.
9. Molderings GJ, Gothert M, van Ahlen H, et al. Modulation of noradrenaline release in human corpus cavernosum by presynaptic prostaglandin receptors. *Int J Impotence Res.* 1992; 4:19-25.
10. Morales A. Nonsurgical management options in impotence. *Hosp Pract.* 1993; 30:15-24.
11. Moreland RB, Traish A, McMillin MA, et al. PGE₁ suppresses the induction of collagen synthesis by transforming growth factor- β_1 in human corpus cavernosum smooth muscle. *J Urol.* 1995; 153:826-834
12. Morley JE, Kaiser FE. Impotence: the internist's approach to diagnosis and treatment. *Adv Intern Med.* 1993; 38:151-168.
13. NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. *JAMA.* 1993; 270:83-90.
14. Padma-Nathan H, Hellstrom WJG, Kaiser FE, et al. Treatment of Men with Erectile Dysfunction with Transurethral Alprostadil. *The New England Journal of Medicine.* 1997; 336:1-7

15. van Ahlen H, Peskar BA, Sticht G, et al. Pharmacokinetics of vasoactive substances administered into the human corpus cavernosum. *J Urol.* 1994; 151:1227-1230.
16. Virag R, Shoukry K, Floresco J, et al. Intracavernous self-injection of vasoactive drugs in the treatment of impotence: 8-year experience with 615 cases. *J Urol.* 1991; 145:287-293.