plasma PGE concentration following intravesical administration of the highest dose of MUSE (1000 mcg) was barely detectable (11.4 picograms/mL). In a study of 14 subjects, the plasma PGE levels were not elevated 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-PGE. 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-PGE retains little (1-2%) of the biological activity of PGE. 15-keto-PGE is rapidly reduced at the cytochrome P450 position to form the most abundant metabolite in plasma, 13,14-dihydro,15-keto-PGE (DHK-PGE), which is biologically inactive. The majority of DHK-PGE is further metabolized to smaller prostanoid remnants that are cleared primarily by the kidney and liver. Between 60% and 90% of PGE has been shown to be metabolized after 1 pass through the pulmonary capillary beds.

Clinical Trials: Intraurethral administration of MUSE does not cause intravesical absorption. Sympathetic nerve constricting PGE does not leak, and 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 intravesical 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 intravesical administration.

Pharmacokinetics in Special Populations: Pulmonary Disease: The near-complete pulmonary first-pass metabolism of PGE is the primary factor influencing the systemic pharmacokinetics of MUSE and is a reason that peripheral venous plasma levels are low or undetectable (<2 picograms/mL) after MUSE administration.

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 sobered 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 (68%) 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%) than couples on placebo (41%). 991 patients (63%) on monogamous doses with MUSE achieved 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, drug (cancer chemotherapeutic) erectile dysfunction, and other etiologies of impotence than in Caucasion and non-Caucasian. 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 (inflamation/infection of the glans, 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 hypersensitivity syndrome that results in an increase in the risk of priapism (rigid erection lasting for more than 4 hours).
4. MUSE should not be used in men for whom sexual activity is inadvisable (see General Precautions).

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 dose titration and when using MUSE intraurethral systems, the rate of blood pressure decline was less than 10 mm Hg at 5 minutes and no patient had a rate of blood pressure decline greater than 30 mm Hg. The rate of syncope was approximately 1 per 100 patient-exposures. The effect of MUSE 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.
2. Cardiovascular effects: During in-clinic dosing, patients should be monitored for symptoms of hypotension, and the lowest effective dose of MUSE should be prescribed.
3. Hematologic effects: Patients administering MUSE imporably may be at risk of arterial abraison resulting in minor bleeding or spotting. The incidence of anticoagulant therapy or with bleeding disorders may be at higher risk of bleeding. Patients on anticoagulant therapy have been safely
In clinical trials of MUSE, priapism (rigid erection lasting >8 hours) and prolonged erection (rigid erection lasting 4 hours and <8 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.

6. 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 administration of drugs that can lower blood pressure 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.

7. Drug-Device Interactions: Use of MUSE 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 heterosexual sexual 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 unresolved 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 an unrelenting 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. Partners and patients 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 PGE, but additional amounts may be present from MUSE administration (see CLINICAL PHARMACOLOGY). Partners who have had an undetermined 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 PGE, 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 intrarectal 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 dosages 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 limb deformities and osteosclerosis 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 and viability) and decreased incidence of contractility (in ossification of the entire skeleton) and gross visceral and skeletal malformations (primarily edema, hydrocephaly, anophthalmia/microphthalmia, and skeletal anomalies) was also observed at 2000 mcg/kg/day, a dose that was 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 headache (66%), dizziness (66%), chest pain (36%), nausea (36%), and back pain (36%). 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. The inciting event (increase in blood pressure or 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 (65% 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.

Other drug-related side effects observed during in-clinic titration and home treatment include swelling of the face and legs, decreased vision, breast pain, dizziness, 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

Overdose has not been reported with MUSE. Overdose with MUSE may result in hypotension, persistent penile pain, and possibly priapism (rigid erection lasting >6h). Priapism can result in permanent worsening of erectile function. Patients suspected of overdose 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 stepwise 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:

<table>
<thead>
<tr>
<th>Dosage Strength</th>
<th>NDC Numbers</th>
<th>Identifying Package Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>125 mcg</td>
<td>0037-8110-06</td>
<td>Tan</td>
</tr>
<tr>
<td>250 mcg</td>
<td>0037-8120-06</td>
<td>Green</td>
</tr>
<tr>
<td>500 mcg</td>
<td>0037-8130-06</td>
<td>Blue</td>
</tr>
<tr>
<td>1000 mcg</td>
<td>0037-8140-06</td>
<td>Burgundy</td>
</tr>
</tbody>
</table>

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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