plasma PGE, concentration following intraurethral administration of the highest dose of MUSE (1000 mcg) was rarely detectable (11.4 picograms/mL). In a study of 14 subjects, the plasma PGE, 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-hydroxy 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 site 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 prostaglandin 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.

Efficacy: In intracavernous and intracorporal administration of alprostadil, a portion of the administered 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 intracavernous 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 intracavernous 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 of PGE, are low or undetectable. A portion of the administered dose is transported to the corpora cavernosa. The half-life of alprostadil in humans is short, varying from a few minutes to a few hours.}

Geriatics: 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 switching to 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. 966 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 (53% vs. 19%) than the couples on placebo. 10% of monogamous patients started MUSE treatment 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, cardiovascular disease, or other etiologies on and similar conclusion 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 glans or the penis), severe hypospadias and curvature, and in patients with acute or chronic urethritis.
3. Sickle cell anemia or trait, thrombocytopenia, polycythemia, multiple myeloma: MUSE is contraindicated in patients who are prone to venous thrombosis or who have a hyperviscosity syndrome. MUSE should not be used in men with sickle cell disease and may be at risk of aplastic anemia or severe complications of sickle cell disease. MUSE is contraindicated in men with a 3-month history of no erections adequate for sexual intercourse.
4. MUSE should not be used in men for whom sexual activity is inadvisable (see General Precautions).

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 and dosing should proceed only if the patient is able to remain in the clinic for 15 minutes after 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 may be at risk of urethral abrasion resulting in minor bleeding. Please check with your healthcare provider before using MUSE for any minor bleeding disorders may be at higher risk of bleeding. Patients on anticoagulant therapy have been safely
Adverse Events Reported by 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

<table>
<thead>
<tr>
<th>Event</th>
<th>MUSE</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 486)</td>
<td>(n = 511)</td>
</tr>
<tr>
<td>UROGENITAL SYSTEM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penile Pain</td>
<td>32%</td>
<td>3%</td>
</tr>
<tr>
<td>Urethral Burning</td>
<td>12%</td>
<td>4%</td>
</tr>
<tr>
<td>Minor Urethral Bleeding/Spotting</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Testicular Pain</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>NERVOUS SYSTEM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>RESPIRATORY Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Infection</td>
<td>3%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Other drug-related side effects observed during in-clinic titration and home treatment include swelling of the penis, lower abdominal pain, leg pain, 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 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 application 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:

- 125 mcg: 0037-8110-06, 0037-8110-01
- 250 mcg: 0037-8120-06, 0037-8120-01
- 500 mcg: 0037-8130-06, 0037-8130-01
- 1000 mcg: 0037-8140-06, 0037-8140-01

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). MUSE and MEDA PHARMACEUTICALS are registered trademarks, and the MEDA PHARMACEUTICALS logo is a trademark of Meda AB or a related entity.

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