Peyronie's disease, also known as curvature of the penis or chronic inflammation of the tunica albuginea, is the development of fibrous scar tissue inside the penis that causes curved, painful erections.1 This condition may prevent a man from having sex or may cause erectile dysfunction.2 The curvature associated with Peyronie’s disease may worsen over time.2

Although the exact cause of Peyronie’s disease is not completely understood, it is thought to result from the rupturing of small blood vessels inside the penis, which may have been damaged during sex, during athletic activity, or as the result of an accident.2

The estimated prevalence of Peyronie’s disease ranges from 1% to 23%.3 Although Peyronie’s disease can occur in men of all ages, its prevalence increases with age.2 Heredity may also play a role. Men who have a connective tissue disorder, including Dupuytren’s contracture, a cord-like thickening that causes the fingers to pull inward, may have an increased risk for Peyronie’s disease.2 A number of other factors that may be linked to Peyronie’s disease include hypertension, diabetes, obesity, hyperlipidemia, smoking, and pelvic surgery.4

In addition to interfering with sexual intercourse, Peyronie’s disease may cause anxiety or stress, place strain on the relationship with a sexual partner, or even make fathering a child challenging because intercourse is difficult or impossible.2 The pain, disfigurement, and erectile dysfunction associated with Peyronie’s disease can impose substantial duress on affected men, including a loss of psychosexual well-being.4 For patients whose symptoms are mild, a watchful waiting approach is sometimes recommended.1 For patients whose symptoms are more serious, medication or surgery may be recommended by a physician.1 Surgical procedures, including penile implant, are generally not recommended until the curvature of the penis stops increasing and the patient’s erections have been pain-free for at least 6 months.2

**First Drug Approved for Peyronie’s Disease**

In December 2013, collagenase clostridium histolyticum for injection (Xiaflex; Auxilium Pharmaceuticals) became the first pharmacologic treatment to receive US Food and Drug Administration (FDA) approval for the treatment of Peyronie’s disease in men with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy. Xiaflex, a biologic agent, is made from the protein product of collagenase clostridium histolyticum, a living organism.3

According to Audrey Gassman, MD, Deputy Director, Division of Bone, Reproductive and Urologic Products in the FDA’s Center for Drug Evaluation and Research, the approval of Xiaflex “expands the available treatment options for men experiencing Peyronie’s disease, and enables them, in consultation with their doctor, to choose the most appropriate treatment option.”5

Collagenase clostridium histolyticum was approved by the FDA in 2010 for the treatment of adult patients with Dupuytren’s contracture with a palpable cord.

**Mechanism of Action**

Collagenases are proteinases that hydrolyze collagen in its native triple helical conformation under physiologic conditions, resulting in the lysis of collagen deposits.6

The signs and symptoms of Peyronie’s disease are caused by a collagen plaque. The injection of collagen clostridium histolyticum into a Peyronie’s plaque, which is comprised mostly of collagen, may result in the enzymatic disruption of the plaque. After this disruption of the plaque, penile curvature deformity and the patient bother caused by Peyronie’s disease are reduced.6

**Dosing and Administration**

Collagenase clostridium histolyticum should be administered by a healthcare provider who is experienced in the treatment of male urologic diseases. Collagenase clostridium histolyticum lyophilized powder should be reconstituted with only the supplied diluent before use.

A treatment cycle consists of 2 collagenase clostridium histolyticum injection procedures and a penile modeling procedure. A penile injection must be induced; a single intracavernosal injection of 10 mcg or 20 mcg of alprostadil may be used for this purpose.6

With the penis in the erect state, the target area in the Peyronie’s plaque to be injected must be identified and marked. The penis should be in a flaccid state before collagenase clostridium histolyticum is injected. On each of 2 days, 1 to 3 days apart, 0.58 mg of collagenase clostridium histolyticum is injected into the plaque.
target plaque, according to the injection procedure.

A penile modeling procedure is performed 1 to 3 days after the second injection of each treatment cycle. For each plaque causing the curvature deformity, up to 4 treatment cycles may be administered. Each treatment cycle may be repeated at approximately 6-week intervals. If the curvature deformity is less than 15 degrees after the first, second, or third treatment cycle, or if further treatment is not clinically indicated, then subsequent treatment cycles should not be administered. This treatment is available as a single-use glass vial containing 0.9 mg of collagenase clostridium histolyticum as a sterile, lyophilized powder for reconstitution. It is also available as a sterile diluent in a single-use glass vial.

### Clinical Studies

The efficacy of collagenase clostridium histolyticum was evaluated in 2 randomized, double-blind, placebo-controlled trials of 832 adult men with Peyronie’s disease (Study 1 and Study 2). To be included in the study, patients had to have penile curvature deformity of at least 30 degrees in the stable phase of Peyronie’s disease. Patients were excluded if they had a ventral curvature deformity, an isolated hourglass deformity, or a calcified plaque that could have interfered with the injection technique. At baseline, penile pain was either not present or was mild in most (98%) patients.

Patients received up to 4 treatment cycles of collagenase clostridium histolyticum or of placebo (weeks 0, 6, 12, 18), and were followed in a non-treatment follow-up period (weeks 24–52). In each treatment cycle, 2 injections of collagenase clostridium histolyticum or 2 injections of placebo were administered 1 to 3 days apart. A penile modeling procedure was performed on patients at the study site 1 to 3 days after the second injection of the cycle. The treatment cycle was repeated at approximately 6-week intervals for up to 3 additional times, for a maximum of 8 total injection procedures and 4 total modeling procedures. Patients were also instructed to perform penile modeling at home for 6 weeks after each treatment cycle.

The coprimary end points in Study 1 and Study 2 were the percent change from baseline to week 52 in penile curvature deformity and the change in the bother domain score of the Peyronie’s Disease Questionnaire from baseline to week 52. The bother domain score is a composite of patient-reported items, including concern about erection pain, erection appearance, and the impact of Peyronie’s disease on intercourse and on the frequency of intercourse.

Patients with Peyronie’s disease receiving collagenase clostridium histolyticum had significantly improved penile curvature deformity compared with patients receiving placebo (Table 1). Moreover, the improvement in curvature deformity was numerically similar among patients with baseline curvature deformity from 30 degrees to 60 degrees and those with curvature deformity from 61 degrees to 90 degrees.

Patients receiving collagenase clostridium histolyticum also had a significant reduction in patient-reported bother associated with Peyronie’s disease compared with patients receiving placebo (Table 2). The reduction in the bother domain score was numerically similar between patient groups stratified by degree of baseline curvature deformity (30-60 degrees and 61-90 degrees).

### Safety

The safety data for collagenase clostridium histolyticum were obtained from controlled and uncontrolled clinical studies in 1044 patients with Peyronie’s disease who received a total of 7466 injections of collagenase clostridium histolyticum.

The most common (≥25%) adverse reactions reported in patients treated with collagenase clostridium histolyticum and at an incidence greater than in patients receiving placebo were penile hematoma, penile swelling, and penile pain.

### Warnings and Precautions

**Boxed warning.** The prescribing information for collagenase clostridium histolyticum contains a boxed warning stating that corporal rupture (penile fracture) was reported as an adverse reaction in 5 of 1044 (0.5%) patients treated with this drug in clinical studies. In 9 (0.9%) of the patients, a diagnosis of corporal rupture cannot be excluded. Severe penile hematoma was also

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**Table 1** Collagenase Clostridium Histolyticum: Median Percent Change in Penile Curvature Deformity from Baseline to Week 52

<table>
<thead>
<tr>
<th>Penile curvature</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Collagenase clostridium histolyticum (N = 199)</td>
<td>Collagenase clostridium histolyticum (N = 202)</td>
</tr>
<tr>
<td></td>
<td>Placebo (N = 104)</td>
<td>Placebo (N = 107)</td>
</tr>
<tr>
<td>Baseline</td>
<td>Mean percent change, treatment difference, 95% CI, and P value were based on an analysis of variance model with factors for treatment, stratum of baseline penile curvature, and their interaction using last observation carried forward in the modified intent-to-treat population. CI indicates confidence interval. Source: Xiaflex (collagenase clostridium histolyticum) for injection prescribing information; 2013.</td>
<td></td>
</tr>
<tr>
<td>Mean percent change, %</td>
<td>–35</td>
<td>–33.2</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(–26.7 to –7.6)</td>
<td>(–19.5 to –3.3)</td>
</tr>
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reported as an adverse reaction in 39 (3.7%) patients treated with collagenase clostridium histolyticum. The boxed warning also states that collagenase clostridium histolyticum is available for the treatment of Peyronie’s disease only through a restricted Risk Evaluation and Mitigation Strategy program.6

Contraindications. Collagenase clostridium histolyticum is contraindicated in patients with Peyronie’s plaques that involve the penile urethra and in patients with a history of severe allergic reaction to this drug or to collagenase used in other applications.6

Tendon rupture or serious injury. Collagenase clostridium histolyticum should not be injected into tendons, nerves, blood vessels, or other collagen-containing structures of the hand. Injection into these structures may result in possible permanent injury, such as tendon rupture or ligament damage.6

Serious injury to the penis. Collagenase clostridium histolyticum should not be injected into the urethra, nerves, blood vessels, corpora cavernosa, or other collagen-containing structures of the penis. Injection into these structures may result in possible permanent injury, such as corporal rupture (penile fracture).6

Allergic reactions. Healthcare providers should be prepared to address severe allergic reactions after collagenase clostridium histolyticum injections.6

Patients with abnormal coagulation. Collagenase clostridium histolyticum should be used with caution in patients with abnormal coagulation, including patients who have received anticoagulant medications, other than low-dose aspirin, within 7 days of the injection.6

Drug interactions. Collagenase clostridium histolyticum should be used with caution in patients receiving anticoagulant therapies, except for low-dose aspirin.

Use in Specific Populations

Pregnancy. There are no adequate and well-controlled studies of collagenase clostridium histolyticum in pregnant women. Collagenase clostridium histolyticum should only be used during pregnancy if clearly needed.6

Nursing mothers. It is not known whether collagenase clostridium histolyticum is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when collagenase clostridium histolyticum is administered to a nursing woman.6

Pediatric use. The safety and effectiveness of collagenase clostridium histolyticum in pediatric patients aged <18 years have not been established.6

Geriatric use. Of the 551 patients receiving collagenase clostridium histolyticum in the clinical trials of Peyronie’s disease, 100 (18%) were aged ≥65 years and 5 (0.9%) were aged ≥75 years. No overall differences in safety were observed in these patients.6

Table 2

<table>
<thead>
<tr>
<th>Bother domain score</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagenase clostridium histolyticum (N = 199)</td>
<td>Placebo (N = 104)</td>
<td>Collagenase clostridium histolyticum (N = 202)</td>
</tr>
<tr>
<td>Baseline mean, degrees</td>
<td>7.5</td>
<td>7.4</td>
</tr>
<tr>
<td>Mean change, %</td>
<td>–2.8</td>
<td>–1.6</td>
</tr>
<tr>
<td>Treatment difference, % (95% CI)</td>
<td>–1.2b (–2.4 to –0.03)</td>
<td>–1.1b (–2.1 to –0.002)</td>
</tr>
</tbody>
</table>

*Mean change, treatment difference, 95% CI, and P value were based on an analysis of variance model with factors for treatment, stratum of baseline penile curvature, and their interaction using last observation carried forward in the modified intent-to-treat population.

P < .05.

CI indicates confidence interval.

Source: Xiaflex (collagenase clostridium histolyticum) for injection prescribing information; 2013.

Conclusion

The recent FDA approval of a new indication for collagenase clostridium histolyticum marks the availability of the first pharmacologic treatment option for men with Peyronie’s disease, which is the only alternative to surgery. This approval offers patients with Peyronie’s disease who are not candidates for a surgical procedure a new, and the only, noninvasive approach to therapy. Treatment with collagenase clostridium histolyticum showed a significant improvement in penile curvature deformity in patients with Peyronie’s disease and a significant reduction in patient-reported bother associated with Peyronie’s disease.

The most frequent adverse reactions reported in ≥25% of patients treated with collagenase clostridium histolyticum and at an incidence greater than in patients receiving placebo were penile hematoma, penile swelling, and penile pain.

References