Endo Announces Updated XIAFLEX® Label with Recurrence and Retreatment Data in Patients with Dupuytren's Contracture

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DUBLIN, May 15, 2015 /PRNewswire/ -- Endo Pharmaceuticals Inc., a subsidiary of Endo International plc (NASDAQ: ENDP) (TSX: ENL), today announced that the U.S. Food and Drug Administration (FDA) has approved a label update for XIAFLEX® (collagenase clostridium histolyticum or CCH) for the treatment of adult Dupuytren's contracture (DC) patients with a palpable cord. The updated label now includes a long-term, observational study demonstrating the rate of recurrence for up to 5 years after successful treatment with XIAFLEX®, and the efficacy and safety of retreatment in patients with recurrent DC.

DC is a chronic condition affecting the hand in which abnormal buildup of collagen can cause the fingers to bend and be drawn in toward the palm. It is a rare genetic condition affecting up to 7 percent of adults in the United States.[1] An estimated 20 to 60 percent of cases may recur following treatment.[2]

"The FDA's initial approval of XIAFLEX® more than five years ago brought an effective, non-surgical and minimally-invasive option for the treatment of adult DC patients," said Sue Hall, Ph.D., Executive Vice President, Chief Scientific Officer and Global Head of Research & Development and Quality at Endo. "Safety and contracture recurrence are important concerns for DC patients and their physicians. The updated label that includes data in patients with recurring contractures coupled with the five-year follow-up data in previously-treated patients further supports the efficacy and safety of XIAFLEX® for initial and retreatment of DC patients."[3]

The long-term, observational study (referred to as Study 4 in the product label) evaluated the recurrence of contracture and safety at Year 2 to Year 5 in patients who had received up to 8 single injections of XIAFLEX® in a previous open-label or double-blind with open-label extension study. A total of 645 patients were enrolled, of whom 30 percent discontinued the study. Recurrence was assessed in successfully treated joints (i.e., a reduction in contracture to 5 degrees or less 30 days after the last injection of XIAFLEX®) and was defined as an increase in joint contracture by at least 20 degree in the presence of a palpable cord, or the joint underwent medical or surgical intervention primarily to correct a new or worsening DC in that joint. Following successful treatment, the probability of remaining recurrence free was 80 percent at Year 2 and 50 percent at Year 5.

The second study (referred to as Study 5 in the product label) evaluated a subset of patients from Study 4 for a joint that was previously successfully treated but had recurrence. Patients in this study received up to 3 injections of XIAFLEX®. Of the 91 patients eligible for the study, 52 enrolled. In the study, 65 percent of recurrence in the metacarpophalangeal (MP) joints (i.e., the knuckle between the hand and the finger) and 45 percent of recurrence in the proximal interphalangeal (PIP) joints (i.e., middle joint of a finger) achieved clinical success after retreatment. No new safety signals were identified among subjects who were retreated with XIAFLEX®.

About Dupuytren's Contracture (DC)
DC is a progressive condition affecting the hand, specifically the layer of tissue just under the skin of the palm and fingers. While this layer of tissue normally contains collagen, in patients with DC there is an increase in the amount of collagen produced. Abnormal collagen build-up results in nodule and cord formation that worsens over time. Eventually, rope-like collagen cords may form, thicken and shorten, affecting the joints and causing the fingers to be drawn in toward the palm. This thickening and shortening of the Dupuytren's cord can reduce the finger joint's range of motion (how much a person can move or straighten them). Once the Dupuytren's collagen cord can be felt, it is referred to as a "palpable cord."

About XIAFLEX®
XIAFLEX® (collagenase clostridium histolyticum, or CCH) is a biologic approved in the U.S., EU, Canada and Australia for the treatment of adult Dupuytren's contracture (DC) patients with a palpable cord, and approved in the United States. for the treatment of adult men with Peyronie's disease (PD) with a palpable plaque and penile curvature deformity of at least 30 degrees at the start of therapy. XIAFLEX® consists of a combination of two subtypes of collagenase, derived from Clostridium histolyticum. Together, the collagenase sub-types are thought to work synergistically to break the bonds of the triple helix collagen structure. XIAFLEX® has been granted Orphan status in the United States by the FDA for DC and PD. Since 2010, it is estimated that more than 60,000 Dupuytren's contracture patients have been treated with XIAFLEX®.[4]

IMPORTANT SAFETY INFORMATION
What is XIAFLEX®?
XIAFLEX® is approved for two uses: Dupuytren's contracture and Peyronie's disease.
XIAFLEX® is a prescription medicine used to treat adults with Dupuytren's contracture when a "cord" can be felt.

XIAFLEX® is a prescription medicine used to treat adult men with Peyronie's disease who have a "plaque" that can be felt and a curve in their penis greater than 30 degrees when treatment is started.

It is not known if XIAFLEX® is safe and effective in children under the age of 18.

Who should not receive XIAFLEX®?
Do not receive XIAFLEX® if you:

- Have been told by your healthcare provider that the Peyronie's plaque to be treated involves the "tube" that your urine passes through (urethra).
- Have had an allergic reaction to collagenase clostridium histolyticum or any of the ingredients in XIAFLEX®, or to any other collagenase product. See the end of the Medication Guide for a complete list of ingredients in XIAFLEX®.

What is the most important information I should know about XIAFLEX® for the treatment of Dupuytren's contracture?
XIAFLEX® can cause serious side effects, including:

- **Tendon rupture or ligament damage.** Receiving an injection of XIAFLEX® may cause damage to a tendon or ligament in your hand and cause it to break or weaken. This could require surgery to fix the damaged tendon or ligament. Call your healthcare provider right away if you have trouble bending your injected finger (towards the wrist) after the swelling goes down or you have problems using your treated hand after your follow-up visit.
- **Nerve injury or other serious injury of the hand. Call your healthcare provider right away** if you get numbness, tingling, or increased pain in your treated finger or hand after your injection or after your follow-up visit.
- **Allergic reactions.** Severe allergic reactions can happen in people who receive XIAFLEX®, because it contains foreign proteins.

Call your healthcare provider right away if you have any of these symptoms of an allergic reaction after an injection of XIAFLEX®:

- Hives
- Swollen face
- Breathing trouble
- Chest pain

What is the most important information I should know about XIAFLEX® for the treatment of Peyronie's disease?
XIAFLEX® can cause serious side effects, including:

- **Penile fracture (corporal rupture) or other serious injury to the penis.** Receiving an injection of XIAFLEX® may cause damage to the tubes in your penis called the corpora. After treatment with XIAFLEX®, one of these tubes may break during an erection. This is called a corporal rupture or penile fracture. This could require surgery to fix the damaged area. Damage to your penis might not get better after a corporal rupture.
- After treatment with XIAFLEX®, blood vessels in your penis may also break, causing blood to collect under the skin (hematoma). This could require a procedure to drain the blood from under the skin.
  Symptoms of corporal rupture or other serious injury to your penis may include:
  - a popping sound or sensation in an erect penis
  - sudden loss of the ability to maintain an erection
  - pain in your penis
  - purple bruising and swelling of your penis
  - difficulty urinating or blood in the urine

  Call your healthcare provider right away if you have any of the symptoms of corporal rupture or serious injury to the penis listed above.
  Do not have sex or have any other sexual activity for at least 2 weeks after the second injection of a treatment cycle with XIAFLEX® and after any pain and swelling has gone away.

XIAFLEX® for the treatment of Peyronie's disease is only available through a restricted program called the XIAFLEX® Risk Evaluation and Mitigation Strategy (REMS) Program. For more information about the XIAFLEX® REMS Program go to www.XIAFLEXREMS.com or call 1-877-942-3539.

2. **Allergic reactions.** Severe allergic reactions can happen in people who receive XIAFLEX, because it contains foreign proteins.

Call your healthcare provider right away if you have any of these symptoms of an allergic reaction after an injection of XIAFLEX®:

- Hives

- Swollen face
- Breathing trouble
- Chest pain

XIAFLEX® when used for either Dupuytren's contracture or Peyronie's disease can cause serious side effects, including:

- **Increased chance of bleeding.** Bleeding or bruising at the injection site can happen in people who receive XIAFLEX®. Talk to your healthcare provider if you have a problem with your blood clotting. XIAFLEX® may not be right for you.

The most common side effects with XIAFLEX® for the treatment of Dupuytren's contracture include:

- Swelling of the injection site or the hand
- Bruising or bleeding at the injection site
- Pain or tenderness of the injection site or the hand
- Swelling of the lymph nodes (glands) in the elbow or armpit (axilla)
- Itching
- Breaks in the skin
- Redness or warmth of the skin
- Pain in the armpit

The most common side effects with XIAFLEX® for the treatment of Peyronie's disease include:

- A small collection of blood under the skin at the injection site (hematoma)
- Swelling at the injection site or along your penis
- Pain or tenderness at the injection site, along your penis and above your penis
- Penis bruising
- Itching of your penis or scrotum (genitals)
- Painful erection
- Erection problems (erectile dysfunction)
- Changes in the color of the skin of your penis
- Blisters at the injection site
- Pain with sex
- A lump at the injection site (nodule)

Tell your healthcare provider if you have any side effect that bothers you or does not go away.
These are not all of the possible side effects with XIAFLEX®. For more information, ask your healthcare provider or pharmacist.

Please see the full Prescribing Information and Medication Guide available at www.XIAFLEX.com.

About Endo International plc
Endo International plc is a global specialty pharmaceutical company focused on improving patients' lives while creating shareholder value. Endo develops, manufactures, markets and distributes quality branded pharmaceutical and generic pharmaceutical products as well as over-the-counter medications through its operating companies. Endo has global headquarters in Dublin, Ireland, and U.S. headquarters in Malvern, PA. Learn more at www.endo.com.

About Endo Pharmaceuticals Inc.
Endo Pharmaceuticals Inc. is focused on developing and delivering high-value branded pharmaceutical products that meet the unmet needs of patients. Endo Pharmaceuticals is an operating company of Endo International plc (NASDAQ: ENDP) (TSX: ENL), a global specialty pharmaceutical company focused on improving patients' lives while creating shareholder value. Learn more at www.endo.com or www.endopharma.com.

Cautionary Note Regarding Forward-Looking Statements

This press release contains "forward-looking statements," including but not limited to the statements by Dr. Hall, as well as statements regarding the safety, efficacy, market and product potential, and other statements regarding XIAFLEX®. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or unknown risks or uncertainties materialize, actual results could vary materially from Endo's expectations and projections. Risks and uncertainties include, among other things, general industry and pharmaceutical market conditions; technological advances and patents attained by competitors; challenges inherent in the research and development process; challenges related to new product marketing, such as the unpredictability or market acceptance for new pharmaceutical products and new indications for such products; and governmental laws and regulations affecting domestic and foreign operations. Endo expressly disclaims any intent or obligation to update these forward-looking statements except as required by law. Additional information concerning these and other risks can be found in press releases issued

by Endo, as well as in Endo's public filings with the U.S. Securities and Exchange Commission and Canadian securities regulators, including the discussion under the heading "Risk Factors" in Endo's Annual Report on Form 10-K and any subsequent Quarterly Reports on Form 10-Q. Copies of Endo's press releases and additional information about Endo are available at www.endo.com.

XIAFLEX is a registered trademark of Endo Global Ventures.

[1]	DiBenedetti DB, Nguyen D, Zografos L, et. al. Prevalence , incidence, and treatments of Dupuytren's disease in the United States: results from a population-based study. Hand. 2011;6:149–158. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3092891/
[2]	Hay DC, Louie DL, Earp BE, et. al. Surgical findings in the treatment of Dupuytren's disease after initial treatment with clostridial collagenase (Xiaflex). *J Hand Surg Eur*. 2013 May. DOI: 10.1177/1753193413488305
[3]	Hindocha S, Stanley JK, Watson S, Bayat A., Dupuytren's diathesis revisited: Evaluation of prognostic indicators for risk of disease recurrence. J Hand Surg Am. 2006 Dec;31(10):1626-34
[4]	Data on file. Specialty pharmacy vial per patient analysis. April 2015. Auxilium Pharmaceuticals, Inc.

To view the original version on PR Newswire, visit:http://www.prnewswire.com/news-releases/endo-announces-updated-xiaflex-label-with-recurrence-and-retreatment-data-in-patients-with-dupuytrens-contracture-300084367.html

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