Endo Pharmaceuticals Presents New Phase 2 Data Evaluating the Safety and Effectiveness of XIAFLEX® (Collagenase Clostridium Histolyticum) for Dupuytren's Disease Nodules

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Study Participants in the Higher Dose Groups Treated with a Single Injection of XIAFLEX® Showed Statistically Significant Decrease in Size and Hardness of Dupuytren's Disease Nodules, a Pre-Cursor Condition to Dupuytren's Contracture

DUBLIN, Sept. 30, 2016 /PRNewswire/ -- Endo Pharmaceuticals Inc., a subsidiary of Endo International plc (NASDAQ: ENDP) (TSX: ENL), today announced new data to be presented evaluating the safety and efficacy of XIAFLEX®(collagenase clostridium histolyticum) (or CCH) injection under investigation for the treatment of palmar Dupuytren's disease nodules. The findings will be presented during a podium presentation on Saturday, October 1, 2016 at 10:40 a.m. CDT at the annual meeting of the American Society for Surgery of the Hand (ASSH) held from September 29 to October 1, 2016 in Austin, Texas.

In a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging study, in 75 adult study participants with Dupuytren's disease and at least 1 nodule who received a single injection of CCH 0.40 mg or 0.60 mg, a statistically significant decrease was shown from baseline in the mean nodule surface area ($P \leq 0.001$), consistency score ($P < 0.001$) and hardness score ($P \leq 0.01$) at week 8 versus study participants receiving placebo. The safety profile of those treated with CCH was generally well tolerated. Adverse events included extremity pain, axillary pain, injection site-related adverse events and pruritus. One adverse event was reported as severe (injection site pain with CCH 0.60 mg). No patients were discontinued from the study because of an adverse event.

The majority of study participants receiving higher doses of CCH were satisfied with their treatment and outcomes – 88.9 percent of 18 study participants in the 0.40 mg CCH group and 83.3 percent of 18 study participants in the 0.60 mg CCH group were "very satisfied" or "quite satisfied" with treatment at week 8 compared to placebo. Similarly, the investigators' global assessment showed an improvement in study participants versus placebo.

"Currently, no treatment has been approved by the U.S. Food and Drug Administration (FDA) for palmar nodules associated with Dupuytren's disease, although many nodules may be a pre-cursor to full Dupuytren's contracture," said Bronier Costas, M.D., orthopedic surgeon at The Hand and Upper Extremity Center of Georgia and the lead study investigator. "These study findings could be an encouraging indicator that treatment with agents that disrupt collagen formation may help reduce nodule size and consistency, and merit further investigation."

In this eight-week, double-blind trial, palpable palmar nodules on 75 adults with Dupuytren's disease and at least 1 palmar nodule were selected for treatment. Study participants were randomized to receive CCH 0.25 mg (n=22), 0.40 mg, or 0.60 mg (n=18, respectively) and then allocated to active treatment (CCH) or placebo (n=16). A single injection into the selected nodule was performed on Day 1. Starting at Week 1, all study participants were instructed to massage the nodule twice daily until Week 4. Efficacy and safety assessments were conducted throughout the study. Investigator-reported nodular consistency and hardness were evaluated at Weeks 1, 4, and 8. Investigator-rated patient improvement (1 [very much improved] to 7 [very much worse]) and patient satisfaction (1 [very satisfied] to 5 [very dissatisfied]) were assessed at week 8.

"XIAFLEX® continues to be the only FDA-approved treatment of adult patients with Dupuytren's contracture with a palpable cord," said Sue Hall, Ph.D., Endo's Executive Vice President, Chief Scientific Officer and Global Head of Research & Development and Quality. "We are encouraged that these new data showed a beneficial effect for patients with Dupuytren's nodules and the potential for improvement in symptoms and discomfort. We continue to be excited by these data and other potential indications for XIAFLEX®."

About Dupuytren's Disease

Dupuytren's disease is a common fibroproliferative disease of the palmar fascia [1] that occurs in approximately 1% to 32% of individuals in Western countries. [2,3] It is characterized by thickening and shortening of fibrous cords within the hand that impact the finger joints (particularly metacarpophalangeal and proximal interphalangeal joints of the ring and small fingers) and while it can start with the appearance of palmar nodules, often leads to flexion contraction and reduced function, also known as Dupuytren's contracture.[4] Dupuytren's disease exhibits 3 clinical phases known as the proliferative, contractile, and residual phases.

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 buildup 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 80,000 patients with Dupuytren's contracture have been treated with XIAFLEX®. [5]

IMPORTANT SAFETY INFORMATION FOR XIAFLEX® (DUPUYTREN'S CONTRACTURE)

INDICATION
XIAFLEX® is indicated for the treatment of adult patients with Dupuytren's contracture with a palpable cord.

IMPORTANT SAFETY INFORMATION FOR XIAFLEX®

- XIAFLEX® is contraindicated in patients with a history of hypersensitivity to XIAFLEX® or to collagenase used in any other therapeutic application or application method
- In the controlled and uncontrolled portions of clinical trials in Dupuytren's contracture, flexor tendon ruptures occurred after XIAFLEX® injection. Injection of XIAFLEX® into collagen-containing structures such as tendons or ligaments of the hand may result in damage to those structures and possible permanent injury such as tendon rupture or ligament damage. Therefore, XIAFLEX® should be injected only into the collagen cord with a MP or PIP joint contracture, and care should be taken to avoid injecting into tendons, nerves, blood vessels, or other collagen-containing structures of the hand. When injecting a cord affecting a PIP joint of the fifth finger, the needle insertion should not be more than 2 to 3 mm in depth and avoid injecting more than 4 mm distal to the palmar digital crease
- Other XIAFLEX®-associated serious local adverse reactions in the controlled and uncontrolled portions of the studies included pulley rupture, ligament injury, complex regional pain syndrome (CRPS), sensory abnormality of the hand, and skin laceration (tear). In a historically controlled post-marketing trial, the incidence of skin laceration (22%) was higher for subjects treated with two concurrent injections of XIAFLEX® compared with subjects treated with up to three single injections in the placebo-controlled premarketing trials (9%). Cases of skin laceration requiring skin graft after finger extension procedures have been reported post-marketing. Signs or symptoms that may reflect serious injury to the injected finger/hand should be promptly evaluated because surgical intervention may be required
- In the controlled portions of the clinical trials in Dupuytren's contracture, a greater proportion of XIAFLEX®-treated patients (15%) compared to placebo-treated patients (1%) had mild allergic reactions (pruritus) after up to 3 injections. The incidence of XIAFLEX®-associated pruritus increased after more XIAFLEX® injections in patients with Dupuytren's contracture
- Because XIAFLEX® contains foreign proteins, severe allergic reactions to XIAFLEX® can occur. Anaphylaxis was reported in a post-marketing clinical study in one patient who had previous exposure to XIAFLEX® for the treatment of Dupuytren's contracture. Healthcare providers should be prepared to address severe allergic reactions following XIAFLEX® injections
- In the XIAFLEX® trials in Dupuytren's contracture, 70% and 38% of XIAFLEX®-treated patients developed an ecchymosis/contusion or an injection site hemorrhage, respectively. Patients with abnormal coagulation (except for patients taking low-dose aspirin, eg, up to 150 mg per day) were excluded from participating in these studies. Therefore, the efficacy and safety of XIAFLEX® in patients receiving anticoagulant medications (other than low-dose aspirin, eg, up to 150 mg per day) within 7 days prior to XIAFLEX® administration is not known. In addition, it is recommended to avoid use of XIAFLEX® in patients with coagulation disorders, including patients receiving concomitant anticoagulants (except for low-dose aspirin)
- In the XIAFLEX® clinical trials for Dupuytren's contracture, the most common adverse reactions reported in ≥25% of patients treated with XIAFLEX® and at an incidence greater than placebo were edema peripheral (eg, swelling of the injected hand), contusion, injection site hemorrhage, injection site reaction, and pain in the injected extremity

IMPORTANT SAFETY INFORMATION FOR XIAFLEX® (PEYRONIE'S DISEASE)
INDICATION
XIAFLEX® is indicated for the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.

IMPORTANT SAFETY INFORMATION FOR XIAFLEX®

WARNING: CORPORAL RUPTURE (PENILE FRACTURE) OR OTHER SERIOUS PENILE INJURY IN THE TREATMENT OF PEYRONIE'S DISEASE
Corporal rupture (penile fracture) was reported as an adverse reaction in 5 of 1044 (0.5%) XIAFLEX®-treated patients in clinical studies. In other XIAFLEX®-treated patients (9 of 1044; 0.9%), a combination of penile ecchymoses or hematoma, sudden penile detumescence, and/or a penile "popping" sound or sensation was reported, and in these cases, a diagnosis of corporal rupture cannot be excluded. Severe penile hematoma was also reported as an adverse reaction in 39 of 1044 (3.7%) XIAFLEX®-treated patients.

Signs or symptoms that may reflect serious penile injury should be promptly evaluated to assess for corporal rupture or severe penile hematoma which may require surgical intervention.

Because of the risks of corporal rupture or other serious penile injury, XIAFLEX® is available for the treatment of Peyronie's disease only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the XIAFLEX® REMS Program.

- XIAFLEX® is contraindicated in the treatment of Peyronie's plaques that involve the penile urethra due to potential risk to this structure and in patients with a history of hypersensitivity to XIAFLEX® or to collagenase used in any other therapeutic application or application method
- Injection of XIAFLEX® into collagen-containing structures such as the corpora cavernosa of the penis may result in

damage to those structures and possible injury such as corporal rupture (penile fracture). Therefore, XIAFLEX® should be injected only into the Peyronie's plaque and care should be taken to avoid injecting into the urethra, nerves, blood vessels, corpora cavernosa or other collagen-containing structures of the penis
- In the double-blind, placebo-controlled portions of the clinical trials in Peyronie's disease, a greater proportion of XIAFLEX®-treated patients (4%) compared to placebo-treated patients (1%) had localized pruritus after up to 4 treatment cycles (involving up to 8 XIAFLEX® injection procedures). The incidence of XIAFLEX®-associated pruritus was similar after each injection regardless of the number of injections administered
- Because XIAFLEX® contains foreign proteins, severe allergic reactions to XIAFLEX® can occur. Anaphylaxis was reported in a post-marketing clinical trial in one patient who had previous exposure to XIAFLEX® for the treatment of Dupuytren's contracture. Healthcare providers should be prepared to address severe allergic reactions following XIAFLEX® injections. The safety of more than one treatment course of XIAFLEX® is not known
- In the XIAFLEX® controlled trials in Peyronie's disease, 65.5% of XIAFLEX®-treated patients developed penile hematoma, and 14.5% developed penile ecchymosis. Patients with abnormal coagulation (except for patients taking low-dose aspirin, eg, up to 150 mg per day) were excluded from participating in these studies. Therefore, the efficacy and safety of XIAFLEX® in patients receiving anticoagulant medications (other than low-dose aspirin, eg, up to 150 mg per day) within 7 days prior to XIAFLEX® administration is not known. In addition, it is recommended to avoid use of XIAFLEX® in patients with coagulation disorders, including patients receiving concomitant anticoagulants (except for low-dose aspirin)
- In the XIAFLEX® clinical trials for Peyronie's disease, the most frequently reported adverse drug reactions (≥25%) and at an incidence greater than placebo included: penile hematoma, penile swelling, and penile pain

Please see the full Prescribing Information, including Boxed Warning and Medication Guide, available at www.XIAFLEX.com.

1. Warwick D, Thomas A, Bayat A. Dupuytren's disease: overview of a common connective tissue disease with a focus on emerging treatment options. *Int J Clin Rheumatol*. 2012;7(3):309-323.
2. Lanting R, Broekstra DC, Werker PM, van den Heuvel ER. A systematic review and meta-analysis on the prevalence of Dupuytren disease in the general population of Western countries. *Plast Reconstr Surg*. 2014;133(3):593-603.
3. Dibenedetti DB, Nguyen D, Zografos L, Ziemiecki R, Zhou X. Prevalence, incidence, and treatments of Dupuytren's disease in the United States: results from a population-based study. *Hand (N Y)*. 2011;6(2):149-158.
4. Picardo NE, Khan WS. Advances in the understanding of the aetiology of Dupuytren's disease. Surgeon. 2012;10(3):151-158.
5. Data on file. DOF-XDC-19. Endo Pharmaceuticals Inc.; July 2016.

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 Drs. Costas and 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.

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SOURCE Endo International plc

Endo International plc: Investors/Media: Keri P. Mattox, (484) 216-7912; Media: Heather Zoumas-Lubeski, (484) 216-6829