Endo Launches First Generic Version of Pylera® (bismuth subcitrate potassium, metronidazole, tetracycline hydrochloride) Capsules

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DUBLIN, March 10, 2023 /PRNewswire/ -- Endo International plc (OTC: ENDPQ) announced today that one of its operating companies, Par Pharmaceutical, Inc., has begun shipping the first generic version of Allergan's Pylera® (bismuth subcitrate potassium, metronidazole, tetracycline hydrochloride) 140 mg, 125 mg and 125 mg capsules in the U.S., following final approval from the U.S. Food and Drug Administration of its Abbreviated New Drug Application.

"We're proud to be a reliable, quality supplier providing choices to healthcare professionals and their appropriate patients," said Scott Sims, Senior Vice President and General Manager, Injectable Solutions & Generics at Endo. "This first-to-market generic product strengthens our portfolio and is a lower-cost option for people who need the medication."

Bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride capsules, in combination with omeprazole, are indicated for the treatment of patients with Helicobacter pylori infection and duodenal ulcer disease (active or history of within the past five years) to eradicate H. pylori.

According to IQVIA ™, Pylera® sales were approximately $30 million for the 12 months ended December 31, 2022.

Pylera® is a registered trademark of Aptalis Pharma Canada ULC, an Allergan affiliate.

IMPORTANT SAFETY INFORMATION FOR BISMUTH SUBCITRATE POTASSIUM, METRONIDAZOLE AND TETRACYCLINE HYDROCHLORIDE CAPSULES

WARNING: POTENTIAL FOR CARCINOGENICITY **Metronidazole has been shown to be carcinogenic in mice and rats. It is unknown whether metronidazole is associated with carcinogenicity in humans**

CONTRAINDICATIONS
Methoxyflurane: Bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride. the concurrent use of tetracycline hydrochloride, a component of bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride reported to result in fatal renal toxicity.
Disulfiram: Bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride psychotic reactions have been reported in alcoholic patients who are using metronidazole, a component of bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride.
Alcohol: Alcoholic beverages or other products containing propylene glycol should not be consumed during and for at least 3 days after therapy with bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride occur due to the interaction between alcohol or propylene glycol and metronidazole, a component of bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride.
Cockayne Syndrome: Bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride is contraindicated in patients with Cockayne Syndrome. Severe irreversible hepatotoxicity/acute liver failure with fatal outcomes have been reported after initiation of metronidazole in patients with Cockayne Syndrome.
Severe Renal Impairment: Bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride is contraindicated in patients with severe renal impairment. The antianabolic action of the tetracyclines may cause an increase in blood urea nitrogen (bun). In patients with significantly impaired renal function, higher serum concentrations of tetracyclines may lead to azotemia, hyperphosphatemia, and acidosis.
Pregnancy: Bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride is contraindicated during pregnancy.
Hypersensitivity Reactions: Bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride is contraindicated in patient with known hypersensitivity (e.g. urticaria, erythematous rash, flushing and fever) to bismuth subcitrate potassium, metronidazole or other nitroimidazole derivatives, or tetracyclines.

WARNINGS AND PRECAUTIONS

Fetal Toxicity: Tetracycline can cause fetal harm when administered to a pregnant woman. Based on animal data, use of drugs of the tetracycline class during the second and third trimester of pregnancy can cause permanent discoloration of the teeth (yellow-gray brown) and possibly inhibit bone development. If bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride is used during pregnancy, or if the patient becomes pregnant while taking bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride, advise the patient of the potential risk to the fetus.
Maternal Toxicity: Tetracycline, a component of bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride, administered during pregnancy at high doses (> 2 g iv) was associated with rare but serious cases of maternal hepatotoxicity. This syndrome may result in stillborn or premature birth due to maternal pathology.
Tooth Enamel Discoloration and Hypoplasia: The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term use of the drug, but has been observed following repeated short-term courses.
Central and Peripheral Nervous System Effects:
Metronidazole: convulsive seizures, encephalopathy, aseptic meningitis and peripheral neuropathy (including optic neuropathy) have been reported. CNS symptoms are generally reversible within days to weeks upon discontinuation of metronidazole. CNS lesions seen on MRI have also been described as reversible. Aseptic meningitis symptoms may occur within hours of dose administration and generally resolve after metronidazole therapy is discontinued.
Tetracycline: intracranial hypertension (IH), including pseudotumor cerebri, has been associated with the use of tetracyclines. Clinical manifestations of IH include headache, blurred vision, diplopia, and vision loss; papilledema can be found on fundoscopy. Women of childbearing age who are overweight or have a history of IH are at greater risk for developing tetracycline associated IH. Concomitant use of isotretinoin should be avoided because isotretinoin is also known to cause IH.
Bismuth-containing products: cases of neurotoxicity associated with excessive doses of various bismuth-containing products have been reported. Effects have been reversible with discontinuation of bismuth therapy.
Development of Potential for Microbial Overgrowth: Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with metronidazole and requires treatment with an antifungal agent. As with other antibacterial drugs, use of tetracycline hydrochloride may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, discontinue bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride and institute appropriate therapy.
Photosensitivity: Photosensitivity, manifested by an exaggerated sunburn reaction, has been observed in patients taking tetracycline. Instruct patients taking bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride to avoid exposure to the sun or sun lamps. Discontinue treatment at the first evidence of skin erythema.
Darkening of the Tongue and/or Black Stool: Bismuth subcitrate potassium may cause temporary and harmless darkening of the tongue and/or black stools, generally reversible within several days after treatment *[see Adverse Reactions]*. Stool darkening should not be confused with melena.
Use in Patients with Blood Dyscrasias: Metronidazole is a nitroimidazole, and should be used with care in patients with evidence of or history of blood dyscrasia. Total and differential leukocyte counts are recommended before and after therapy.
Increased Drug Plasma Concentrations in Patients with Hepatic Impairment: Patients with mild to moderate hepatic impairment should be monitored for metronidazole associated adverse events. Bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride is not recommended in patients with severe hepatic impairment.
Cutaneous Reactions: Skin and subcutaneous disorders including Stevens-Johnson Syndrome, toxic epidermal necrolysis and dress syndrome (drug rash with eosinophilia and systemic symptoms) have been reported. Discontinue treatment at the first evidence of a cutaneous reaction.

ADVERSE REACTIONS
Most frequently reported adverse reactions (>5o): abnormal feces, diarrhea, nausea, and headache.

DRUG INTERACTIONS
Methoxyfurane: risk of fatal renal toxicity; do not co-administer.
Disulfram: psychotic reactions can occur; do not take concurrently or within the last 2 weeks of disulfram.

- Alcohol: abdominal cramps, nausea, vomiting, headaches, and flushing can occur; do not consume during therapy and for at least 3 days afterwards.
- Oral contraceptives: decreased efficacy possibly resulting in pregnancy; use a different or additional form of contraception.
- Anticoagulants: potentiation of the anticoagulant effect; prothrombin time, international normalized ratio (INR), or other suitable anticoagulation tests should be closely monitored.
- Lithium: increased lithium serum concentrations; measure serum lithium and serum creatinine concentrations during therapy.
- Antacids, multivitamins or dairy products: decreased absorption of bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride; do not take concomitantly.
- Busulfan: increased busulfan serum concentrations; avoid concomitant use, monitor for busulfan toxicity.
- CYP inducers and CYP inhibitors: prolonged or accelerated half-life of metronidazole or concomitant medications; use with caution.

INDICATION
Bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride capsules in combination with omeprazole are indicated for the treatment of patients with Helicobacter pylori infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate H. pylori. The eradication of Helicobacter pylori has been shown to reduce the risk of duodenal ulcer recurrence.

Please see **Full Prescribing Information, including Boxed Warning.** for bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride.

About Endo
Endo (OTC: ENDPQ) is a specialty pharmaceutical company committed to helping everyone we serve live their best life through the delivery of quality, life-enhancing therapies. Our decades of proven success come from passionate team members around the globe collaborating to bring treatments forward. Together, we boldly transform insights into treatments benefiting those who need them, when they need them. Learn more at

www.endo.com or connect with us on LinkedIn.

About Par Pharmaceutical
Par Pharmaceutical develops, manufactures and markets innovative and cost-effective generic pharmaceutical and branded injectable products that help improve patients' lives. Par, among the top leaders in the U.S. generics industry, possesses an expanding portfolio that includes sterile injectables, alternative dosage forms and other differentiated products. Par Pharmaceutical is an Endo company. Learn more at www.parpharm.com.

Cautionary Note Regarding Forward-Looking Statements
Certain information in this press release may be considered "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995 and any applicable Canadian securities legislation, including, but not limited to, the statements by Mr. Sims, any statements relating to product launch, shipments, sales potential, quality, safety or cost. and any statements that refer to expected, estimated or anticipated future results or that do not relate solely to historical facts. Statements including words or phrases such as "believe," "expect," "anticipate," "intend," "estimate," "plan," "will," "may," "look forward," "intend," "guidance," "future," "potential" or similar expressions are forward-looking statements. All forward-looking statements in this communication reflect the Company's current views as of the date of this communication about its plans, intentions, expectations, strategies and prospects, which are based on the information currently available to it and on assumptions it has made. Actual results may differ materially and adversely from current expectations based on a number of factors, including, among other things, the outcome of the Company's contingency planning and restructuring activities; the timing, impact or results of any pending or future litigation, investigations, proceedings or claims, including opioid, tax and antitrust related matters; any actual or contingent liabilities; settlement discussions or negotiations; the Company's liquidity, financial performance, cash position and operations; the risks and uncertainties associated with chapter 11 proceedings; the time, terms and ability to confirm a sale of the Company's businesses under Section 363 of the U.S. Bankruptcy Code; the risk that the Company's chapter 11 cases may be converted to cases under chapter 7 of the Bankruptcy Code; the adequacy of the capital resources of the Company's businesses and the difficulty in forecasting the liquidity requirements of the operations of the Company's businesses; the unpredictability of the Company's financial results; the Company's ability to discharge claims in chapter 11 proceedings; negotiations with the holders of the Company's indebtedness and its trade creditors and other significant creditors; the risks and uncertainties with performing under the terms of the restructuring support agreement and any other arrangement with lenders or creditors while in chapter 11 proceedings; the performance, including the approval, introduction, and consumer and physician acceptance of new products and the continuing acceptance of currently marketed products; and the Company's ability to obtain and successfully manufacture, maintain and distribute a sufficient supply of products to meet market demand in a timely manner. The Company expressly disclaims any intent or obligation to update these forward-looking statements, except as required to do so by law.

Additional information concerning risk factors, including those referenced above, can be found in press releases issued by the Company, as well as the Company's public periodic filings with the U.S. Securities and Exchange Commission and with securities regulators in Canada, including the discussion under the heading "Risk Factors" in the Company's most recent Annual Report on Form 10-K and any subsequent Quarterly Reports on Form 10-Q or other filings with the U.S. Securities and Exchange Commission. Copies of the Company's press releases and additional information about the Company are available at www.endo.com or you can contact the Company's Investor Relations Department at relations.investor@endo.com.

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