Johnson & Johnson

New Study Shows Tapentadol Extended Release (ER) May Significantly Reduce Average Pain Intensity for Diabetic Patients Suffering from Painful Peripheral Neuropathy

Raritan, NJ - January 28, 2011 - New research has been published indicating that patients suffering from a painful complication of diabetes may experience a significant improvement in their pain as measured by a pain intensity scale when using an investigational pain medication. This phase III study, which evaluates the safety and efficacy of tapentadol ER against placebo for relieving moderate to severe chronic pain associated with diabetic peripheral neuropathy (DPN), is published in the January issue of the journal *Current Medical Research and Opinion* (CMRO). An online version of the article may be found here [http://informahealthcare.com/doi/abs/10.1185/03007995.2011.537589].

Just this past week, the Centers for Disease Control and Prevention (CDC) announced there are now nearly 26 million people in the United States living with diabetes. Over time, they can develop a type of nerve damage called neuropathy. Approximately 60 to 70 percent of people with diabetes have some form of neuropathy. The most common type is DPN, which causes pain or loss of feeling in the toes, feet, legs, hands, and arms. It is estimated that painful DPN affects 10 to 20 percent of all patients with diabetes, and many patients on current treatments still experience considerable pain.

"What's encouraging is that at the beginning of this study, the average pain rating across the entire group of patients was severe, but after three weeks on tapentadol ER, the average pain score dropped substantially to a range considered to be mild pain," said Bruce Moskovitz, MD, Therapeutic Area Leader for Pain, Ortho-McNeil-Janssen Scientific Affairs, LLC. "After double-blind randomization, the group of patients that stayed on tapentadol ER maintained its pain reduction, while the group that switched to placebo experienced a significant increase in its average pain score."

About the Study
This trial had two main phases: a 3-week, open-label phase, during which all patients were titrated to their individually optimal tapentadol ER dose (100-250 mg two times per day), followed by a 12-week, double-blind maintenance phase, during which patients were randomized either to continue taking tapentadol ER (at their optimal dose) or to receive placebo.

The primary efficacy endpoint of the study was to measure the change in average pain intensity, as determined by a twice-daily, 11-point pain rating scale or numerical rating scale (NRS; 0='no pain,' 10='pain as bad as you can imagine'), from the point of randomization. Safety was also assessed throughout the study.

At the start of the 3-week, open-label phase, the majority of patients (79.4%) reported severe pain (?6 on the 11-point NRS) with a mean pain intensity of 7.3. By the end of the open-label phase, the mean pain intensity was reduced to 3.5. Following randomization, over the double-blind treatment phase to week 12, pain increased in the placebo group (as demonstrated by the average change in pain intensity of 1.4), while in the tapentadol ER group, pain relief was maintained, as indicated by the change in pain intensity value of 0.0. The mean difference between the tapentadol ER and placebo groups in the change in average pain intensity was -1.3 on the 11-point NRS (95 percent CI; $p<0.001$, tapentadol ER vs. placebo). Researchers observed statistically significant differences in favor of tapentadol ER using all imputation methods.

In a secondary analysis, where rates of those who responded to treatment were calculated, 53.6 percent of patients receiving tapentadol ER and 42.2 percent of patients receiving placebo ($p=0.017$) experienced at least a 30 percent improvement in pain intensity measured from pre-titration to week 12 of the double-blind treatment period.

The patient's global impression of change (PGIC) provided an additional secondary analysis where patients evaluated on a 7-point rating scale their overall status at the end of treatment relative to the beginning of trial treatment (NRS; 1='very much improved,' 7='very much worse'). At the end of double-blind treatment, 64.4 percent of patients receiving tapentadol ER and 38.4 percent of patients receiving placebo reported that their overall status was 'very much improved' or 'much improved' ($p<0.001$) on the PGIC.

In addition, from the start to the end of the open-label titration phase, 60.5 percent (356/588) of patients reported at least a 30 percent improvement in pain intensity.

This phase III, randomized-withdrawal trial evaluated the safety and efficacy of tapentadol ER for relieving painful DPN versus placebo in 588 patients. Patients had at least a 3-month history of opioid and/or non-opioid analgesic use for DPN, dissatisfaction with current treatment, and an average pain intensity score of at least 5 on the 11-point NRS.

The most common treatment-emergent adverse events (TEAEs) during the open-label phase were nausea (21.4 percent), dizziness (15.8), somnolence (15.1), constipation (10.7), vomiting (8.0), headache (7.8), fatigue (7.0), and pruritus (6.6). In the

double-blind period with tapentadol ER, the most common TEAEs that occurred included nausea (13.8 percent), anxiety (9.2), diarrhea (8.2), and dizziness (7.7). During the double-blind treatment period, the overall incidence of TEAEs was similar for male and female patients who received tapentadol ER, and the overall incidence of TEAEs was likewise similar for patients under 65 years of age and over 65 years of age who received tapentadol ER during double-blind treatment.

The safety profile of tapentadol ER in this study, especially the incidence of nausea, vomiting, and constipation during the open-label phase, was similar to previous findings from other phase III, randomized, double-blind efficacy and safety trials of tapentadol ER for nociceptive pain, including chronic low back and osteoarthritic pain. Also in the current study, the mean percentage of days on treatment with tapentadol ER that patients experienced nausea, vomiting, and constipation, respectively, was relatively low in both the open-label (8.8, 2.2 and 5.4 percent) and, particularly, in the double-blind (2.9, 1.0 and 1.9 percent) phases.

Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&JPRD) and Grünenthal GmbH, conducted this study, which J&JPRD has included as part of its New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for tapentadol ER tablets for the management of moderate to severe chronic pain in patients 18 years of age or older. The FDA currently is reviewing this application and, if approved, PriCara®, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., will market tapentadol ER in the United States.

About tapentadol
Tapentadol is a centrally acting oral analgesic that binds to mu-opioid receptors and inhibits norepinephrine re-uptake. Although the exact mechanism of action is not known, these two mechanisms, which affect established pain pathways, are thought to be responsible for pain relief with tapentadol. The tapentadol molecule is classified as Schedule II of the Controlled Substances Act.

NUCYNTA® (tapentadol immediate release) was approved by the FDA on November 20, 2008, and is available by prescription only for the relief of moderate to severe acute pain in patients 18 years of age or older. On December 1, 2009, J&JPRD submitted its New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for tapentadol extended release (ER) tablets for the management of moderate to severe chronic pain in patients 18 years of age or older [http://www.jnj.com/connect/news/product/20091201_200000]. The tapentadol ER tablet formulation is designed to provide a high degree of mechanical resistance, such as to crushing or chewing. The NDA filing is part of the ongoing commitment of J&JPRD and PriCara® to bring new and innovative products to patients and physicians for the treatment and management of pain.

In October 2010, J&JPRD announced it had received a Complete Response letter from the FDA regarding its NDA for tapentadol extended release tablets [http://www.jnj.com/connect/news/product/FDA-Issues-Complete-Response-Letter-to-Johnson-and-Johnson-Pharmaceutical-Research-Development-Regarding-New-Drug-Application-for-Tapentadol-Extended-Release]. J&JPRD is working to address the FDA's requests as quickly as possible. No new clinical studies were requested by the agency.

IMPORTANT SAFETY INFORMATION FOR NUCYNTA® (tapentadol immediate release)

Contraindications

Like other drugs with mu-opioid agonist activity, NUCYNTA® is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma or hypercapnia in unmonitored settings or in the absence of resuscitative equipment. NUCYNTA® is contraindicated in patients who have or are suspected to have paralytic ileus. NUCYNTA® is also contraindicated in patients currently using or within 14 days of using monoamine oxidase inhibitors (MAOIs) due to potential additive effects on norepinephrine levels, which may result in adverse cardiovascular events.

Warnings & Precautions
Respiratory depression is the primary risk of mu-opioid agonists. Respiratory depression occurs more frequently in elderly or debilitated patients and in those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction, in whom even moderate therapeutic doses may significantly decrease pulmonary ventilation. NUCYNTA® should be administered with caution to the elderly, debilitated patients, and patients with conditions accompanied by hypoxia, hypercapnia or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, CNS depression, or coma. In such patients, even usual therapeutic doses of NUCYNTA® may increase airway resistance and decrease respiratory drive to the point of apnea. Alternative non-mu-opioid agonist analgesics should be considered and NUCYNTA® should be employed only under careful medical supervision at the lowest effective dose in such patients. If respiratory depression occurs, it should be treated as any mu-opioid agonist-induced respiratory depression.

Patients receiving other mu-opioid agonist analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives,

hypnotics, or other CNS depressants (including alcohol) concomitantly with NUCYNTA® may exhibit additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, coma or death may result if these drugs are taken in combination with NUCYNTA®. When such combined therapy is contemplated, a dose reduction of one or both agents should be considered.

Opioid analgesics can raise cerebrospinal fluid pressure as a result of respiratory depression with carbon dioxide retention. Therefore, NUCYNTA® should not be used in patients susceptible to the effects of raised cerebrospinal fluid pressure such as those with head injury and increased intracranial pressure. Opioid analgesics may obscure the clinical course of patients with head injury due to effects on pupillary response and consciousness. NUCYNTA® should be used with caution in patients with head injury, intracranial lesions, or other sources of preexisting increased intracranial pressure.

NUCYNTA® is a mu-opioid agonist and is a Schedule II controlled substance. Such drugs are sought by drug abusers and people with addiction disorders. Diversion of Schedule II products is an act subject to criminal penalty. NUCYNTA® can be abused in a manner similar to other mu-opioid agonists, legal or illicit. This should be considered when prescribing or dispensing NUCYNTA® in situations where the physician or pharmacist is concerned about an increased risk of misuse and abuse. All patients treated with mu-opioid agonists require careful monitoring for signs of abuse and addiction. NUCYNTA® may be abused by crushing, chewing, snorting or injecting the product. These practices pose a significant risk to the abuser that could result in overdose and death.

Experience with NUCYNTA® overdose is very limited. Management of overdose should be focused on treating symptoms of mu-opioid agonism. Primary attention should be given to reestablishment of a patent airway and institution of assisted or controlled ventilation when overdose of NUCYNTA® is suspected. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

Patients should be cautioned that NUCYNTA® may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. This is to be expected especially at the beginning of treatment, at any change of dosage as well as in combination with alcohol or tranquilizers.

NUCYNTA® has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. NUCYNTA® should be prescribed with care in patients with a history of a seizure disorder or any condition that would put the patient at risk of seizures.

The development of a potentially life-threatening serotonin syndrome may occur with use of SNRI products, including NUCYNTA®, particularly with concomitant use of serotonergic drugs such as SSRIs, SNRIs, TCAs, MAOIs and triptans, and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

Withdrawal symptoms may occur if NUCYNTA® is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely, hallucinations. Withdrawal symptoms may be reduced by tapering NUCYNTA®.

Pregnancy Category C. There are no adequate and well-controlled studies of NUCYNTA® in pregnant women. NUCYNTA® should be used during pregnancy ONLY if the potential benefit justifies the potential risk to the fetus. NUCYNTA® is not recommended for use in women during and immediately prior to labor and delivery. Neonates whose mothers have been taking NUCYNTA® should be monitored for respiratory depression. NUCYNTA® should not be used during breastfeeding.

NUCYNTA® is not recommended in patients with severe renal or hepatic impairment. NUCYNTA® should be used with caution in patients with moderate hepatic impairment. Like other drugs with mu-opioid agonist activity, NUCYNTA® may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis.

Adverse Events

The most common adverse events are nausea, dizziness, vomiting, somnolence and headache. To see the NUCYNTA® full prescribing information, go to http://www.nucynta.com/nucynta/assets/Nucynta-PI.pdf.

PriCara®, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.

PriCara®, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., is a major health care company in the United States dedicated to the needs of primary care providers who serve a vital role on the frontline of medicine. For more information about the company, please visit www.PriCara.com.

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

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