

FOR IMMEDIATE RELEASE



**SHIONOGI INC. ANNOUNCES PUBLICATION OF DATA IN *PEDIATRICS*
DEMONSTRATING EFFICACY OF KAPVAY™ (clonidine hydrochloride) EXTENDED-
RELEASE TABLETS AS ADD-ON THERAPY TO STIMULANTS FOR THE TREATMENT OF
ADHD IN CHILDREN AND ADOLESCENTS**

FLORHAM PARK, NJ (May 9, 2011) – Shionogi Inc., the U.S.-based group company of Shionogi & Co., Ltd., today announced the publication in *Pediatrics* of data demonstrating the efficacy of non-stimulant KAPVAY™ (clonidine hydrochloride) extended-release tablets when combined with stimulant medications for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents (6-17 years). This study, the first to evaluate KAPVAY in combination with stimulants in ADHD patients with inadequate response to stimulants, showed a significantly greater (40%) improvement in symptoms associated with the condition. The data from the Phase III clinical trial appear in an article in the May 9, 2011, online edition of *Pediatrics*, the medical journal of the American Academy of Pediatrics, in advance of the print edition.

“Nearly one third of the 4.5 million children with ADHD in the U.S. do not achieve optimal response from stimulant monotherapy, therefore a need exists for additional treatment options for this population,” said Matthew Brams, MD, Clinical Assistant Professor, Department of Psychiatry, Baylor College of Medicine, Houston, TX, investigator in the clinical trial and co-author of the *Pediatrics* article. “These study findings suggest that the extended-release version of clonidine hydrochloride, when prescribed as an add-on to stimulants, is useful in reducing ADHD symptoms in children and adolescents ages 6 to 17 with inadequate response to stimulants.”

The eight-week Phase III randomized, double-blind, placebo-controlled trial of 198 children and adolescents (6-17 years) with ADHD demonstrated significant efficacy at Week 5 (primary endpoint) in patients treated with KAPVAY plus stimulant (n=102) compared to a placebo plus stimulant (n=96). Signs and symptoms of ADHD were evaluated using the investigator administered and scored ADHD Rating Scale-IV-Parent Version (ADHDRS-IV) total score.

At Week 5, greater improvement from baseline was observed in the KAPVAY group compared to the placebo group the following scales: ADHD-RS-IV total score (95% CI, -7.83 to -1.13; P=.009) as well as the ADHD-RS-IV hyperactivity/impulsivity and inattention subscale scores (P=.014 and P=.017, respectively). In addition, the study also showed that improvement in the ADHDRS-IV total score from baseline was statistically significant between the KAPVAY group and the placebo group beginning at Week 2 and was maintained during the trial.

“We are very excited to announce the publication of study results of KAPVAY in *Pediatrics* that will provide the ADHD community with data regarding the use of this non-stimulant treatment option,” said Rafael Muniz, MD, Therapeutic Head of U.S. Clinical Development & Medical Affairs at Shionogi Inc. “While KAPVAY is also approved for monotherapy, this study focused on its use as add-on therapy to stimulant medication in a clinically relevant dosing regimen. Shionogi is committed to providing clinical research to physicians, caregivers and patients to support the effective treatment of ADHD.”

The most common adverse reactions (incident at least 5% and twice the rate of placebo) included somnolence (20% KAPVAY, 8% placebo), headache (19% KAPVAY, 21% placebo), fatigue (16% KAPVAY, 4% placebo), upper abdominal pain (12% KAPVAY, 8% placebo) and nasal congestion (9% KAPVAY, 6% placebo). One patient of 102 enrolled in the KAPVAY group discontinued from the study due to an adverse reaction. Of the 96 patients in the placebo plus stimulant group, three discontinued because of adverse reactions. Treatment-emergent adverse events in the KAPVAY group, such as somnolence and fatigue, were generally mild to moderate.

About the Study

- **Design:** Eight-week, double-blind, placebo-controlled trial of KAPVAY 0.1 mg/d to 0.4 mg/d (all doses > 0.1 mg/d administered twice daily) in combination with stimulants (i.e., medications in the amphetamine and methylphenidate classes) in 198 children and adolescents (aged 6-17 years) with hyperactive- or combined-subtype ADHD who had inadequate response to their stable stimulant regimen. KAPVAY and stimulant doses could be titrated to achieve an optimal efficacy and safety profile for each patient.
- **Patient Population:** Children and adolescents (aged 6-17 years) with a diagnosis of predominantly hyperactive- or combined-subtype ADHD, who had a stable regimen of stimulant treatment during the previous four weeks were included. Patients were excluded from participation in the study if they had a current diagnosis or history of a psychiatric disorder that required psychotropic medication or severe comorbid Axis I or Axis II disorder that could interfere with assessment of clonidine efficacy and safety.
- **Assessments:** The primary efficacy measure was improvement from baseline to Week 5 in ADHD-RS-IV total score versus placebo completed by the investigator at screening, baseline, and all weekly visits. The investigators evaluated improvement from baseline for all efficacy measures using analysis of covariance. The safety measures of the study were assessed by spontaneously reported adverse events, vital signs, electrocardiogram recordings, and clinical laboratory values.
- **Results:** Improvement in ADHD-RS-IV total score from baseline was statistically significant between the KAPVAY group and the placebo group beginning at Week 2 and was maintained during the trial. At Week 5, patients in the KAPVAY group experienced a significantly greater improvement from baseline in ADHD-RS-IV total score compared with patients in the placebo group. Treatment-emergent adverse events in the KAPVAY group were generally mild and included somnolence, sedation and fatigue.

About KAPVAY™

KAPVAY (clonidine hydrochloride) extended-release tablets are indicated for the treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications in children and adolescents (ages 6-17). KAPVAY received FDA approval in October 2010 and has been commercially available since January 2011. The efficacy of KAPVAY in the treatment of ADHD is based on the results of this clinical trial as well as another controlled monotherapy trial in children and adolescents ages 6-17 who met DSM-IV criteria for ADHD hyperactive or combined hyperactive/inattentive subtypes. KAPVAY is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, and social) for patients with this syndrome. The effectiveness of KAPVAY for longer-term use (more than 5 weeks) has not been systemically evaluated in controlled trials.

Administered orally, KAPVAY exerts its pharmacological effects as a centrally acting alpha₂-adrenoceptor agonist. The formulation of KAPVAY is designed to delay the absorption of active drug in order to decrease peak to trough plasma concentration differences.

Important Safety Information

KAPVAY should not be used in patients with known hypersensitivity to clonidine.

KAPVAY can cause dose-related decreases in blood pressure and heart rate, use caution in treating patients who have a history of syncope or may have a condition that predisposes them to syncope, such as hypotension, orthostatic hypotension, bradycardia, or dehydration. Use with caution in patients treated concomitantly with antihypertensives or other drugs that can reduce blood pressure or heart rate or increase the risk of syncope.

Somnolence/sedation were commonly reported adverse reactions in clinical studies with KAPVAY. Potential for additive sedative effects with central nervous system (CNS) depressant drugs, advise patients to avoid use with alcohol. Caution patients against operating heavy equipment or driving until they know how they respond to KAPVAY.

Patients should be instructed not to discontinue KAPVAY therapy without consulting their physician due to the potential risk of withdrawal effects. KAPVAY should be discontinued slowly in decrements of no more than 0.1 mg every 3 to 7 days.

In patients who have developed localized contact sensitization or other allergic reaction to clonidine in a transdermal system, substitution of oral clonidine hydrochloride therapy may be associated with the development of a generalized skin rash, urticaria, or angioedema.

Use cautiously in patients with vascular disease, cardiac conduction disease, or chronic renal failure: Monitor carefully and uptitrate slowly.

Clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates or other sedating drugs. Use caution when KAPVAY is administered concomitantly with antihypertensive drugs, due to the additive pharmacodynamics effects (e.g. hypotension, syncope).

KAPVAY should not be used during pregnancy unless clearly needed. Since clonidine hydrochloride is excreted in human milk, caution should be exercised when KAPVAY is administered to a nursing woman.

Caution is warranted in patients receiving clonidine concomitantly with agents known to affect sinus node function or AV nodal conduction (e.g., digitalis, calcium channel blockers and beta-blockers) due to a potential for additive effects such as bradycardia and AV block.

Clonidine, the active ingredient in KAPVAY, is also approved as an antihypertensive. Do not use KAPVAY in patients concomitantly taking other clonidine-containing products, (e.g. Catapres®, JENLOGA, etc.).

Common adverse reactions (incidence at least 5% and twice the rate of placebo) include: Somnolence, fatigue, upper respiratory tract infection, irritability, throat pain, insomnia, nightmares, emotional disorder, constipation, nasal congestion, increased body temperature, dry mouth, and ear pain.

To report SUSPECTED ADVERSE REACTIONS, contact Shionogi Inc. at 1-800-849-9707 ext. 1454 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

For full prescribing information, please visit www.KAPVAY.com.

About ADHD

ADHD is a neurobehavioral disorder that most often occurs in childhood and may continue into adolescence and adulthood. There are three subtypes of ADHD: predominantly hyperactive/impulsive,

predominantly inattentive, and combined hyperactive/impulsive and inattentive, with the latter being the most common. ADHD symptoms can include behaviors such as trouble focusing, frequent daydreaming, excessive talking, fidgeting/squirming, chronic impatience and difficulty waiting their turn, depending on the category.

The cause of ADHD is not yet known. However, research has shown potential links to genetic and environmental factors. While there is no cure for ADHD, the disorder can be managed with a variety of treatments including parental education and training, behavioral therapy and prescription medication.

About Shionogi & Co., Ltd.

Headquartered in Osaka, Japan, Shionogi & Co., Ltd. is a major research-driven pharmaceutical company dedicated to placing the highest value on patients. Shionogi's Research and Development currently targets three therapeutic areas: Infectious Diseases, Pain, and Metabolic Syndrome. The Company has provided such innovative medicines as Crestor and Doripenem, which have been successfully delivered to millions of patients. In addition, Shionogi is engaged in new research areas such as allergy and cancer. Contributing to the health of patients around the world through development in these therapeutic areas is Shionogi's primary goal. For more details, please visit www.shionogi.co.jp. For more information on Shionogi Inc., headquartered in Florham Park, NJ, please visit www.shionogi.com.

Forward Looking Statements

This announcement contains forward-looking statements. These statements are based on expectations in light of the information currently available, assumptions that are subject to risks and uncertainties which could cause actual results to differ materially from these statements. Risks and uncertainties include general domestic and international economic conditions such as general industry and market conditions, and changes of interest rate and currency exchange rate. These risks and uncertainties particularly apply with respect to product-related forward-looking statements. Product risks and uncertainties include, but are not limited to, completion and discontinuation of clinical trials; obtaining regulatory approvals; claims and concerns about product safety and efficacy; technological advances; adverse outcome of important litigation; domestic and foreign healthcare reforms and changes of laws and regulations. Also for existing products, there are manufacturing and marketing risks, which include, but are not limited to, inability to build production capacity to meet demand, unavailability of raw materials and entry of competitive products. The company disclaims any intention or obligation to update or revise any forward-looking statements whether as a result of new information, future events or otherwise.

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