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SHIONOGI INC.

STUDY DATA SHOW CUVPOSA® REDUCED CHRONIC SEVERE DROOLING IN PATIENTS AGES 3-16 YEARS-OLD WITH NEUROLOGIC CONDITIONS

FLORHAM PARK, NJ (January 25, 2012) – Shionogi Inc., the U.S.-based group company of Shionogi & Co., Ltd., today announced results from two studies published online today in the journal *Therapeutics and Clinical Risk Management*: the first study, a randomized, double-blind, placebo-controlled phase III trial, showed that children ages 3-16 with problem drooling due to neurologic conditions demonstrated a significantly better response to CUVPOSA® (glycopyrrolate) oral solution than to placebo.[1] The second study, a multicenter, open-label trial, evaluated the safety and efficacy of CUVPOSA® for over 24 weeks.[2] The majority of patients in this study were between the ages of 3-16 with moderate-to-severe drooling. CUVPOSA® oral solution is the first and only U.S. Food and Drug Administration-approved treatment to reduce chronic severe drooling in patients ages 3-16 with neurologic conditions associated with problem drooling, such as cerebral palsy.

"Chronic severe drooling is a health issue for children with neurologic disorders," said lead study investigator Robert S. Zeller, MD, director, Blue Bird Circle Clinic for Pediatric Neurology at Texas Children's Hospital, Houston, Texas. "These studies reinforce the efficacy and safety, respectively, of CUVPOSA®."

After eight weeks in the first study of 38 patients [CUVPOSA® (n=20), placebo (n=18)], 14 of 19 patients (73.7 percent) in the CUVPOSA® group and three of 17 (17.6 percent) in the placebo group exhibited at least a 3-point improvement on the modified Teacher's Drooling Scale (mTDS) (P=0.0011). Two of the 38 patients were older than 16 and, as such, were excluded from the results. A beneficial effect of CUVPOSA® was observed as early as two weeks after treatment initiation (52.6 percent; P=0.0007), with the proportion of responders increasing continuously through week 8. Mean improvements in mTDS score at week 8 were 3.94 points (SD: 1.95; 95 percent CI 2.97, 4.91; median: 4.30 points) in the CUVPOSA® group and 0.71 points (SD: 2.14; 95 percent CI -0.43, 1.84; median: 0.25 points) in the placebo group (P<0.0001).

Statistically significant differences in the first study were observed for both the investigator and parent/caregiver global assessments of study medication. For patients in the CUVPOSA® group, 84.2 percent of investigators and 100 percent of parent/caregivers agreed that the treatment was worthwhile, compared with 41.2 percent of investigators (P=0.0140) and 56.3 percent of parent/caregivers (P=0.0017) of patients in the placebo group.

"Parents and caregivers of children with neurologic conditions, such as cerebral palsy, can face many challenges," said Jennifer Davidson, DO, medical director, Shionogi Inc. "By treating the severe drooling that is often associated with these conditions, these caregivers can focus their time and resources on other aspects of their children's care. With CUVPOSA®, we are continuing our commitment to help address the unmet medical needs of patients."

All 20 patients treated with CUVPOSA® and 15 of 18 (83.3 percent) who received the placebo had at least one treatment-emergent adverse event (TEAE), including 15 (75 percent) and seven (39 percent), respectively, who had TEAEs considered by the investigator to be related to treatment. Four patients (20 percent) in the CUVPOSA® group, but none in the placebo group, had at least one severe TEAE. The

most common adverse reactions (greater than 30 percent incidence) were dry mouth, constipation, vomiting and nasal congestion. Adverse reactions also included flushing (25 percent) and urinary retention (15 percent).

The second study of 137 intent-to-treat patients was a multicenter, open-label trial evaluating the safety and efficacy of CUVPOSA®. Most patients (n=122; 89 percent) had at least one TEAE, 47 percent of which were deemed related to CUVPOSA®, with most being mild to moderate in intensity. Several TEAEs occurred more frequently in the high (>0.2 mg/kg) and middle (≥0.1 to ≤0.2 mg/kg) than in the low dose (<0.1 mg/kg) group. Fourteen patients had 20 serious AEs, eight while taking the study drug and six within 30 days of the last dose. Of these 20 SAEs, four were considered treatment-related: nystagmus, esophageal candidiasis, dehydration and gastrointestinal motility disorder. The most common treatment-emergent adverse events (incidence >5%) are constipation, vomiting, diarrhea, pyrexia, dry mouth, flushing, and nasal congestion. Nineteen patients (13.9%) discontinued due to an AE, but no AE trend was specifically associated with discontinuation.

After 24 weeks, 52.3 percent (95 percent CI, 43.7 percent–60.9 percent) of patients had a ≥3-point decrease in mTDS from baseline and were classified as responders to treatment with CUVPOSA®. The percentage of the 53 non-naïve patients (i.e., patients previously treated with CUVPOSA®) classified as responders (58.5 percent; 95 percent CI, 45.2 percent–71.8 percent) was higher than that of the 84 naïve patients (48.1 percent; 95 percent CI, 36.9 percent–59.2 percent). At the end of the study, 83.5 percent of parents/caregivers and 85.8 percent of investigators rated CUVPOSA® as a worthwhile treatment.

CUVPOSA® is supplied as a cherry-flavored, liquid solution for oral administration and was FDA approved in the United States in July 2010 and launched commercially in April 2011.

About CUVPOSA®

CUVPOSA® is an anticholinergic indicated to reduce chronic severe drooling in patients ages 3-16 with neurologic conditions associated with problem drooling (e.g., CP). CUVPOSA® indirectly reduces the rate of salivation by preventing stimulation of acetylcholine receptors that are located on certain peripheral tissues, such as salivary glands. CUVPOSA® is dosed on a titration schedule based on weight, therapeutic response and adverse reactions. It must be administered to patients by caregivers using an accurate measuring device. Please see the full prescribing information at www.CUVPOSA.com for administration and dosing instructions.

Important Safety Information About CUVPOSA®

- Contraindicated in conditions that preclude anticholinergic therapy (e.g., glaucoma, paralytic ileus, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis)
- Contraindicated in patients taking solid oral dosage forms of potassium chloride. The passage of potassium chloride tablets through the GI tract may be arrested or delayed with coadministration of Cuvposa
- Constipation is a common dose-limiting adverse reaction and may lead to discontinuation of Cuvposa. Assess patients for constipation, particularly within 4-5 days of initial dosing or after a dose increase. Intestinal pseudoobstruction may present as abdominal distention, pain, nausea, or vomiting
- Incomplete mechanical intestinal obstruction: diarrhea may be an early symptom, especially in patients with ileostomy or colostomy. If obstruction is suspected, discontinue Cuvposa and evaluate

- Avoid patient exposure to high ambient temperatures. Heat prostration (fever and heatstroke due to decreased sweating) can occur with use of anticholinergic drugs such as Cuvposa
- Cuvposa may cause drowsiness or blurred vision; do not engage in age-appropriate activities requiring mental alertness such as operating a motor vehicle or other machinery or performing hazardous work while taking Cuvposa
- Use Cuvposa with caution in patients with conditions that are exacerbated by anticholinergic drug effects including:
  - Autonomic neuropathy, renal disease, ulcerative colitis—large doses may suppress intestinal motility to the point of producing a paralytic ileus and for this reason may precipitate or aggravate "toxic megacolon," a serious complication of the disease; hyperthyroidism, coronary heart disease, congestive heart failure, cardiac tachyarrhythmias, tachycardia, and hypertension; hiatal hernia associated with reflux esophagitis
- Glycopyrrolate reduces GI transit time which may result in altered release of certain drugs when formulated in delayed or controlled-release forms. Cuvposa can increase serum levels of atenolol, metformin and digoxin (slow dissolution tablets; consider other oral dosage forms of digoxin). Dose reductions of atenolol or metformin may be needed
- Cuvposa may decrease serum levels of haloperidol or levodopa. Consider dose increase of levodopa and closely monitor haloperidol patients for worsening of schizophrenic symptoms and development of tardive dyskinesia when coadministered with Cuvposa
- The anticholinergic effects of Cuvposa may be increased with concomitant administration of amantadine. Cuvposa dose reduction should be considered
- Cuvposa is largely renally eliminated. Cuvposa should be used with caution in patients with renal impairment
- The most common adverse reactions (incidence ≥30%) are dry mouth (40%), vomiting (40%), constipation (35%), flushing (30%), and nasal congestion (30%)

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

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

About Cerebral Palsy

Cerebral palsy is a lifelong condition that encompasses a group of non-progressive, neurological disorders affecting body movement and muscle coordination. About 10-30 percent of children with cerebral palsy suffer from excessive drooling.[1]

About Chronic Severe Drooling

Sialorrhea (drooling or excessive salivation) is an unintentional loss of saliva from the mouth.[1]
Drooling is normal in infants, but a significant proportion of the developmentally disabled population experiences drooling caused primarily by neuromuscular dysfunction that makes it hard to swallow.

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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References

1. Zeller, R.S., Lee, H.M, Cavanaugh, P & Davidson, J. (2011). Randomized phase III evaluation of the efficacy and safety of a novel glycopyrrolate oral solution for the management of chronic severe drooling in children with cerebral palsy or other neurologic conditions. *Journal of Therapeutics and Clinical Risk Management.*

2. Zeller, R.S., Davidson, J., Lee, H.M & Cavanaugh, P (2011). A multicenter, open-label, 24-week study assessing the safety and efficacy of glycopyrrolate oral solution for the management of pathologic drooling in pediatric patients with cerebral palsy and other neurologic conditions. *Therapeutics and Clinical Risk Management*.

日本語要約

Shionogi Inc.は、流涎症（よだれ）治療薬 CUVPOSA®（一般名 glycopyrrolate）について、2 つの第 3 相臨床試験結果が、2012 年 1 月 24 日付で医学雑誌 *Therapeutics and Clinical Risk Management* にオンライン掲載されましたので、お知らせいたします。

まず最初に、流涎症を伴う神経疾患を有する 3-16 歳の患者を対象とした 8 週間のプラセボ対照二重盲検試験において、プラセボ投与群に比較し CUVPOSA®投与群で統計学的に有意な流涎症症状の改善効果が認められました。また、プラセボ投与群に比較し、CUVPOSA®投与群の被験者の親または介護者からも統計学的に有意な治療満足度が得られました。
次に、137 例の中等度から重度の流涎症を有する患者に CUVPOSA®内用液を 24 週間投与し 、CUVPOSA®の安全性と有効性を評価したオープンラベル試験では、89%の被験者において少なくとも 1 つの有害事象が観察され、その 47%が CUVPOSA®に関連したものとみなされましたが、そのほとんどは軽度から中程度の有害事象でした。

脳性麻痺は、生涯にわたり身体運動や筋肉の協調運動に障害をもたらす非進行性の神経障害のひとつであり、小児の脳性麻痺患者の約 10-30%は重篤な流涎症を患っています。脳性麻痺のような神経疾患を有する児童の親や介護者の方々は多くの問題に直面していますが、慢性の重篤な流涎症を治療することにより、介護者の方々に対して、他の面での児童のケアに、時間やリソースをかける機会を与えることが可能になります。

CUVPOSA®内用液は、脳性麻痺のような神経疾患を有する 3-16 歳の患者における、慢性で重篤な流涎症に対する唯一の治療薬です。米国において、2010 年 7 月に FDA に承認され、2011 年 4 月より発売されています。