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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Neurontin ® (Gabapen ®)/ Gabapentin

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See United States Package Insert (USPI)

NATIONAL CLINICAL TRIAL NO.: NCT00785772

PROTOCOL NO. : A9451169

PROTOCOL TITLE: A post-marketing clinical pharmacokinetics study of gabapentin in Japanese epileptic subjects with renal impairment

Study Center: 1 center in Japan

Study Initiation Date and Completion Dates: 16 March 2010 to 1 April 2010

Phase of Development: Phase 4

Study Objective(s): To confirm the pharmacokinetics of gabapentin after administration to Japanese epileptic subjects with renal impairment and investigate if there are differences between values obtained from a simulation with a population pharmacokinetic (PK) model that was used as a rationale for dose adjustment in subjects with renal impairment and observed plasma concentration, and to evaluate the safety throughout the study.

METHODS

Study Design: This study was planned as a multicenter, open-label, post-marketing clinical study in epileptic subjects with renal impairment or on hemodialysis. The subjects of the study were epileptic subjects with renal impairment (subjects with a creatinine clearance of 5 to 59 mL/min or who require hemodialysis) who had no deviation from inclusion criteria/exclusion criteria and who consented for study participation. The creatinine clearance was calculated using the Cockcroft-Gault equation. Duration of observation was 15 days from screening if the subject had already been treated with gabapentin and 28 days from screening if the subject was treated with gabapentin for the first time. In case gabapentin treatment was completed or discontinued in the study, the subject was to be observed 7 days after completion or discontinuation of the study as well.

Number of Subjects (Planned and Analyzed):

Planned: 10 subjects

Analyzed: 1 subject

The target sample size of the study was 10 subjects. As a result of a consultation with Pharmaceuticals and Medical Devices Agency, however, the study was completed with an enrollment of 1 subject because prolongation of the study period or a change in the inclusion criteria (the upper limit of age was deleted) did not lead to further enrollment of subjects.

Diagnosis and Main Criteria for Inclusion: Epileptic subjects aged 20 years or older indicated for the treatment with gabapentin (combined therapy with an antiepileptic for partial seizure [including secondary generalized seizure] in epileptic subjects in whom other antiepileptics had been inadequate) with renal impairment defined as a creatinine clearance of 5 to 59 mL/min at baseline or on hemodialysis.

Study Treatment: The study drugs used were GABAPEN® tablets 200 mg, 300 mg, and 400 mg. Descriptions in the package insert were followed as much as possible, and dosage regimens were adjusted depending on the creatinine clearance. However, changes in dose based on clinical symptoms or laboratory test results were allowed during the study.

Efficacy Evaluations: No efficacy evaluations were performed for this study.

Pharmacokinetic Evaluations: Observed plasma gabapentin concentration

Plasma gabapentin concentrations were measured to investigate if there were differences from values obtained from a simulation with a population PK model that was used as a rationale for dose adjustment in subjects with renal impairment.

Safety Evaluations: Adverse events, laboratory tests (including hematology, serum chemistry, and urinalysis), physical examination, blood pressure, pulse rate, body weight

Statistical Methods: In the tabulation of the pharmacokinetic and safety analyses, the day of the start of the study treatment was defined as Day 1.

Pharmacokinetics Analysis: Based on the obtained data on plasma gabapentin concentrations, population mean estimates were simulated by demographic factor and dose for each subject using a currently established population PK model and compared with actual measurements. Individual parameters were also determined by the Bayesian method and the deviations from the population parameters were evaluated.

Safety Analysis: The summaries and lists of safety data and other parameters were tabulated in accordance with the Pfizer Data Standard, which specifies the sponsor's standard methods for data collection and reporting concerning safety information.

RESULTS

Subject Disposition and Demography: A subject who had already been taking gabapentin was enrolled in the study, received study treatment, and completed the study. The demographic factors of this subject were as follows: 62 year-old male, weight 61.8 kg, height 161.00 cm, BMI 23.8 kg/m^2, and duration of epilepsy 5.98 years. The subject was on

hemodialysis, receiving a maintenance dose of 300 mg twice daily. No supplemental dosing was performed immediately after hemodialysis.

Efficacy Results: No efficacy evaluations were performed in this study.

Pharmacokinetic Results: The plasma drug concentration of the subject was 38.4 and 44.64 μg/mL at Visit 2 (Day 8) and Visit 3 (Day 15), respectively. The observed plasma concentration was 2.16- and 2.59-fold of the plasma concentration estimated from the population mean and 1.15- and 1.37-fold of the individual estimate on Day 8 and Day 15, respectively. The observed values were higher than the plasma concentrations calculated from the population means and individual estimates.

Safety Results: No adverse events or laboratory test parameters with significant changes were observed in the study. No clinically significant changes were observed in blood pressures, pulse rate, body weight, or physical findings.

CONCLUSION(S): The observed plasma gabapentin concentrations after administration of gabapentin at 300 mg twice daily to one Japanese epileptic subject (CLcr = 7.49 mL/min) receiving hemodialysis three times a week were higher than the plasma concentrations calculated from the population mean and individual estimates.

No adverse events developed, and no clinically significant changes were observed in the safety evaluation in the study.