OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW - EXECUTIVE SUMMARY

NDA: 21-008 S018	Submission Date(s): 10 November, 2005
Brand Name	Sandostatin LAR® Depot
Generic Name	Octreotide acetate for injectable suspension
Reviewer	Wei Qiu, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPE2
ORM division	Division of Metabolic and Endocrine Products
Sponsor	Novartis
Relevant IND(s)	37,768
Submission Type	Pediatric Exclusivity and Labeling
Formulation; Strength(s)	Injectable suspension; 10, 20, and 30 mg
Indication	Pediatric Hypothalamic Obesity

1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE2) has reviewed NDA 21-008 S 018 submitted on 10 November, 2005 and finds it acceptable. Recommendation should be conveyed to the sponsor as appropriate.

1.2 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The sponsor conducted a randomized, multi-center, double-blind trial (No. SMS995B 2403) of Sandostatin LAR® Depot (40 mg) vs. saline-control in the treatment of pediatric hypothalamic obesity. The performed study with regard to clinical pharmacology has met the Written Request dated January 7, 2004.

(1) The Pharmacokinetic-Pharmacodynamics (PK-PD) under ***Type of Study*** of the Written Request stated that "Serum samples will be collected for octreotide concentration measurement using a population pharmacokinetic approach after the first dose in each patient. Optimally, randomized sparse sampling (i.e., at least 3 samples per patient with reasonably randomized sampling times between patients) should be used for the population approach. In addition, serum samples must be collected for octreotide trough concentration measurements (C_{trough}). Serum insulin concentrations must be measured at the same time points as octreotide concentrations are measured."

In this study, blood samples for determination of octreotide serum concentrations were taken prior to each Sandostatin LAR® dose over the 6-month evaluation period. After the first and prior to

the second Sandostatin LAR® dose, 3 additional fasting blood samples were taken, respectively within 1 to 10 days, 11 to 20 days, and 21 to 30 days post first dose. Blood samples for fasting serum insulin assessment were taken at the same time points as the blood collections for octreotide concentrations.

(2) **PK-PD** Under ***Study endpoints*** stated "Primary pharmacokinetic parameters (i.e., Cmax, AUC, and CL) and parameters for PK-PD models with descriptive summaries. Pharmacokinetic (PK) - Pharmacodynamic (PD) relationship will be explored using concentrations of octreotide and insulin". Under ***Statistical information, including power of study and statistical assessments***, it stated that "Descriptive statistical summary of the primary PK parameters and PK/PD parameters will be presented".

Octreotide concentration vs. time data were presented graphically and by descriptive statistics. Time to steady-state was determined graphically based on the measured trough concentration time profiles. Following monthly i.m. injection of Sandostatin LAR® Depot, accumulation of octreotide concentrations was observed. A steady-state concentration appeared to be achieved after the 3rd dose and was maintained throughout the remaining treatment period. Mean trough octreotide concentrations increased from 1396 pg/mL prior to the 2nd dose to 2973 pg/mL at steady state, representing an approximately 2-fold accumulation. Results were consistent with previous experience in adults where 2-fold accumulation was observed after multiple dosing. Steady state octreotide trough concentrations were correlated with gender ($p = 0.005$). On average, female patients had a 16.6% higher octreotide trough concentration than males.

The sponsor stated that because only limited data were available in the initial phase (the first few days post *i.m.* dose) and none in the terminal phase, it was not considered possible to characterize the initial dose release pattern and the absorption-controlled elimination and, therefore, inappropriate to attempt to model the full time course of the octreotide profile with a population PK model approach. Thus, PK parameters including CL/F, V/F, and AUC were not determined by the sponsor. This reviewer agreed with the sponsor.

PK-PD relationships of Sandostatin LAR Depot in pediatric patients with hypothalamic obesity were evaluated. The relationship between octreotide concentrations and insulin concentrations were explored graphically, and statistical analysis was conducted on octreotide values in logarithmic scale with a linear mixed-effects modeling approach. Results showed that insulin levels were significantly correlated with steady-state octreotide trough concentrations ($p = 0.004$) and treatment ($p = 0.001$). No significant relationship with steady-state octreotide trough concentration was observed when considering only Sandostatin LAR® Depot treated patients ($p=0.93$). Thus, the sponsor concluded that the significant correlation between octreotide trough concentration and insulin concentrations appeared to be solely due to the treatment difference.

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/s/

Hae-Young Ahn

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