

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW**

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

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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 Phase IV Commitments

None.

1.3 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., C_{max} , 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.

2 Question Based Review

2.1 General Attributes of the Drug

1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Sandostatin LAR® Depot (octreotide acetate for injectable suspension) was approved on November 25, 1998 for the treatments of acromegaly, carcinoid tumors, and vasoactive intestinal peptide tumors. Pediatric Written Request Letter was issued on January 7, 2004. In response, the sponsor conducted a randomized, double-blind, multi-center, safety and efficacy study in which pediatric patients with hypothalamic obesity received 40 mg of octreotide or placebo monthly for a minimum of 6 months. This submission contained 6 months of data. The sponsor initiated an extension study per the agreement to provide patients with an additional 6 months of open-label octreotide. The extension study was terminated at the recommendation of the Data Safety Monitoring Board (DSMB). The sponsor planned to submit the data to the Agency upon completion of the clinical study report.

This submission contains assessment of PK and PK-PD of octreotide in pediatric patients with hypothalamic obesity.

2.2 General Clinical Pharmacology

Not applicable.

2.3 Intrinsic Factors

1. What is the PK in pediatric patients with hypothalamic obesity? What is the PK-PD relationship?

A total of 30 pediatric patients with hypothalamic obesity were treated with 40 mg monthly IM injection of Sandostatin LAR® Depot and 30 patients received saline control. Patients had mean age of 13.6 years and range of 6 to 17 years. Blood samples were taken pre-dose throughout the 6 month treatment period. In addition, three blood samples were taken after the first dose in the first month. These samples were taken within 1 to 10 days post-dose, 11 to 20 days post-dose and 21 to 30 days post-dose.

Individual and mean octreotide concentrations by month are presented in **Figure 1** and **Table 1**. Consistent with the pharmacokinetics of Sandostatin LAR® Depot formulation observed in adults, steady-state appeared to be achieved after the 3rd injection. An average trough octreotide concentration of 2973 pg/mL, calculated from all patient data points at steady-state, was maintained throughout the remaining treatment period.

Figure 1. Mean and individual octreotide concentration (pg/mL)

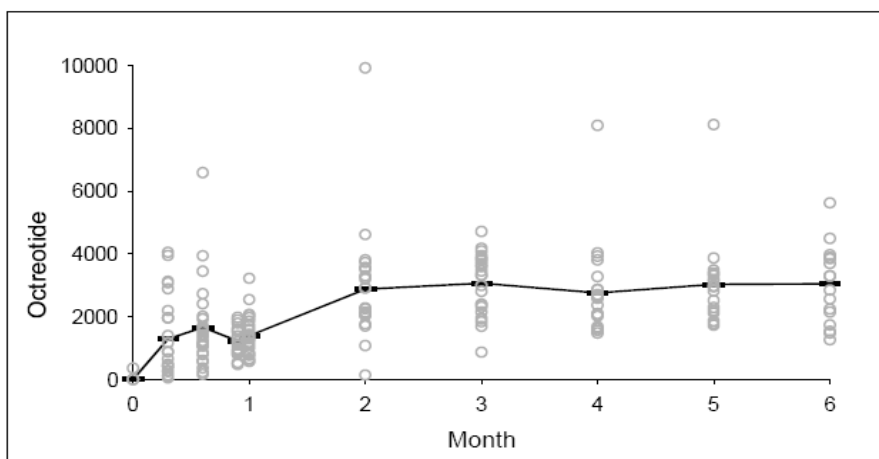


Table 1. Mean and SD of octreotide concentration

Month	Octreotide Concentration (pg/mL)	
	Mean	SD
0	0	0
0.3*	1289	1292
0.6*	1662	1379
0.9*	1226	438
1	1395	640
2	2880	1724
3	3064	973
4	2761	1444
5	3028	1355
6	3045	1211

*concentrations in the 3 intervals are grouped as Month 0.3, 0.6 and 0.9.

The sponsor stated that due to limited data were available in the initial phase (the first few days post IM 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.

The influence of body weight, age, BMI and gender on steady-state octreotide trough concentrations was graphically explored (**Figure 2**).

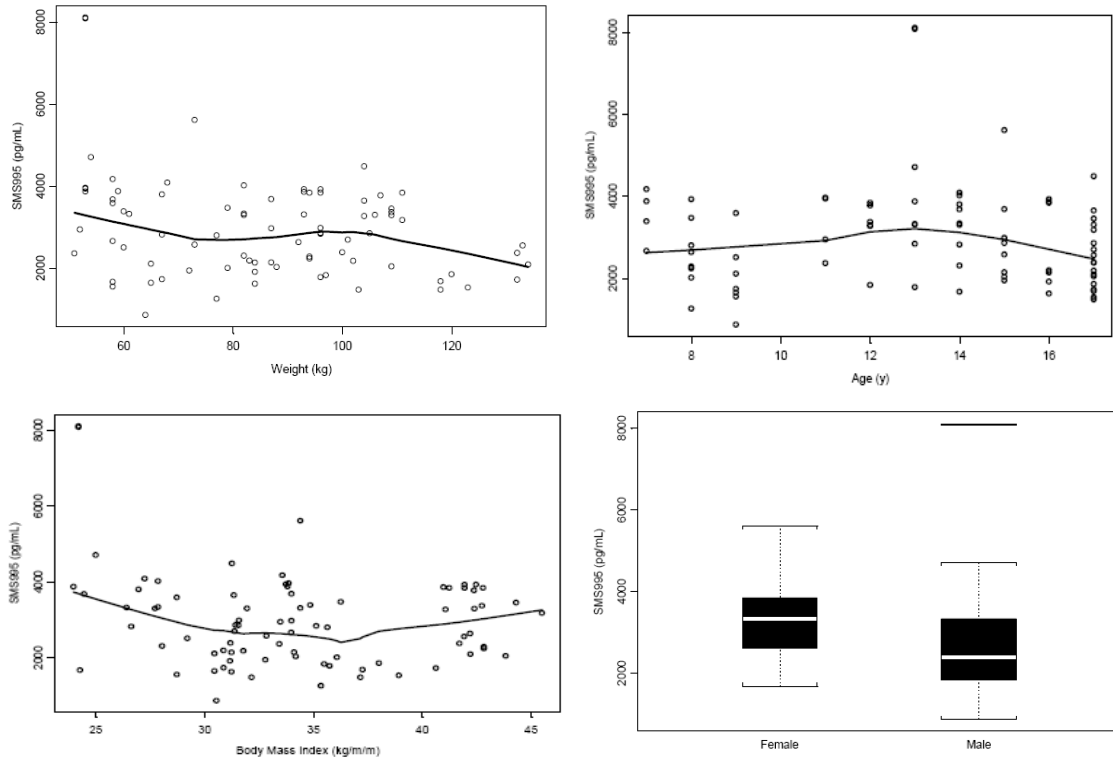


Figure 2. Steady-state octreotide (SMS 995) concentration vs body weight, age, BMI, and gender

Statistical analysis with a linear mixed-effects model approach suggested that steady-state octreotide trough concentration was moderately correlated with body weight (p-value = 0.03) and was significantly correlated with gender (p-value = 0.005). The mean octreotide trough concentrations were 3231 and 2770 pg/mL, respectively, in female and male patients. With the gender effect being accounted for in the analysis, body weight was no longer a significant factor. The difference in mean body weight between male patients (86.6 ± 24.0 kg, range 53.3 – 133 kg) and female patients (84.4 ± 21.5 kg, range 52.3 – 111 kg) was not statistically significant (p = 0.3).

The relationship between octreotide trough concentrations at steady-state vs. the pharmacodynamic marker of effect (insulin level) is presented in **Figure 3**.

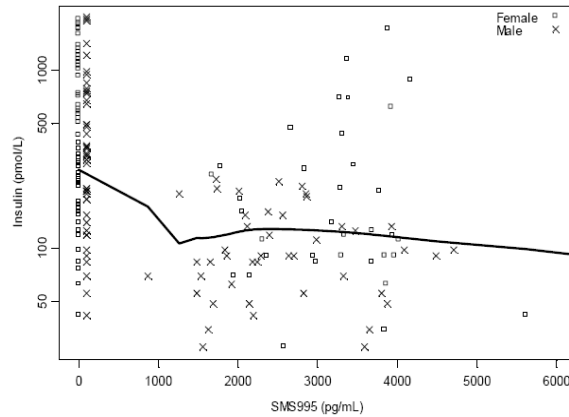


Figure 3. Octreotide (SMS 995) concentration (pg/mL) vs. insulin concentration (pmol/L)

Statistical analysis demonstrated a significant correlation between the octreotide concentration and insulin levels (p-value = 0.004). However, this is only due to the treatment difference, Sandostatin® LAR Depot versus saline control, as no significant relationship between octreotide concentration and insulin levels was observed when considering only Sandostatin® LAR Depot treated patients (p-value = 0.93).

Reviewer's Comments:

Approved package insert stated that after a single IM injection of Sandostatin LAR® Depot to adult healthy subjects or patients with acromegaly, the serum concentrations of octreotide reached an initial transient peak within a day following by a plateau reached about two to three weeks post injection. The plateau concentrations were maintained for two to three weeks. Considering the complex PK profile of this product, this reviewer agrees with the sponsor that it is inappropriate to model the limited data with a population PK approach.

2.4 Extrinsic Factors

Not applicable.

2.5 General Biopharmaceutics

Not applicable.

2.6 Analytical Section

1. What bioanalytical methods are used to assess concentrations?

Octreotide concentration was measured using an immunoassay with a lower limit of quantification of 40 pg/mL.

3 Detailed Labeling Recommendations

Under **CLINICAL PHARMACOLOGY**, Pharmacokinetics, 2. Pharmacokinetics of Sandostatin LAR® Depot, the following paragraph was added by the sponsor:

Sandostatin LAR® Depot has been studied in pediatric patients with hypothalamic obesity. See **Pediatric Use** under **PRECAUTIONS**.

Under **PRECAUTIONS**, Pediatric Use, the sponsor proposed the following:

In pediatric patients with hypothalamic obesity, the mean octreotide concentration after 6 doses of 40 mg Sandostatin LAR® Depot administered by IM injection every four weeks was approximately 3.0 ng/mL. Steady-state concentration was achieved after 3 injections of 40 mg dose.

This reviewer agrees with the sponsor's labeling changes.

4 Appendix

4.1 Individual Study Synopsis

Study synopsis

Title of study:

A randomized, multicenter, double-blind trial of Sandostatin LAR[®] Depot (40 mg) vs. saline-control in the treatment of pediatric hypothalamic obesity.

Investigator(s):

Details in the synopsis of the Clinical Study Report [[CSR 2403](#), [Study Synopsis](#)]

Publication(s):

Details in the synopsis of the Clinical Study Report [[CSR 2403](#), [Study Synopsis](#)]

Study period: first patient enrolled: 17-May-2004 last subject completed: 13-Jul-2005

Objectives:

Clinical Pharmacology Objectives:

- To summarize the steady-state pharmacokinetics (PK) of Sandostatin LAR[®] Depot in pediatric patients with hypothalamic obesity and identify possible covariate effects.
 - To explore the relationship between the octreotide concentration and insulin levels.
-

Design, number of subjects, inclusion criteria, duration of treatment:

Details in the synopsis of the Clinical Study Report [[CSR 2403](#), [Study Synopsis](#)]

Criteria for evaluation:

Pharmacokinetic evaluations

Blood samples for octreotide serum concentrations were taken after a ≥ 8 h fast 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.

Pharmacodynamic evaluations

Blood samples for fasting serum insulin assessments were taken at the same time points as the blood collections for octreotide concentrations.

Statistical methods

Statistical analyses were conducted with PK and PD variables logarithmically transformed when appropriate, as judged by the distributional properties. Octreotide concentration vs. time data were presented graphically and descriptive statistics were provided by day of assessment.

The population for PK analysis consisted of all patients with octreotide concentration data at Month 3-6, considered to be at steady state. The population for PK-PD analysis included the additional patients of the saline-control group. Linear mixed-effect modeling analysis was performed to determine possible covariate effects for steady-state octreotide concentration, including BMI, body weight, gender, and age. PK-PD relationships between octreotide and insulin concentrations were explored graphically, and statistical analysis was conducted on octreotide values in logarithmic scale with a linear mixed-effects modeling approach. Baseline insulin was included in the PK-PD analyses.

Results:

Pharmacokinetics

Of the 60 patients qualified for inclusion in the intent to treat analysis population, 30 received saline control, and 30 received Sandostatin LAR[®] Depot, with 26/30 patients providing octreotide concentration data for PK analysis. 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.

Steady-state octreotide concentrations (in log-scale) were not correlated with either age or BMI, but moderately correlated with body weight (p-value = 0.03) and significantly correlated with gender (p-value = 0.005). Female patients had a mean octreotide concentration which was 16.6% higher than that in males. The correlation with body weight became statistically non-significant when the gender effect was included in the analysis. Mean body weight between the male patients (86.6 ± 24.0 kg) and female patients (84.4 ± 21.5 kg) was not significantly different (p-value = 0.3).

Pharmacokinetic-Pharmacodynamics:

Insulin levels were significantly correlated with steady-state octreotide concentrations (p-value = 0.004) and treatment (p-value = 0.001). No significant relationship with steady-state octreotide concentration was observed when considering only Sandostatin LAR[®] Depot treated patients (p-value = 0.93). Thus, the significant correlation between octreotide concentration and insulin appeared to be solely due to the treatment difference.

Conclusions:

Pharmacokinetics

- Following monthly *i.m.* injections of 40 mg Sandostatin LAR[®] Depot formulation in pediatric patients with hypothalamic obesity, mean octreotide concentrations showed an approximately two-fold accumulation and reached a steady-state value of 2973 pg/mL after the 3rd injection.
- Steady-state trough octreotide concentration was not correlated with age and BMI, but moderately correlated with body weight and was significantly different between male and female patients.

Pharmacokinetic-pharmacodynamic relationship

- Insulin level measured at the time of steady-state octreotide appeared to be significantly different between patients treated with Sandostatin LAR[®] Depot and saline control. However, within the Sandostatin LAR[®] Depot treated group there was no significant concentration-response correlation.

Date of the report: 10-Oct-2005

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/s/

Wei Qiu
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Hae-Young Ahn
4/13/2006 02:00:09 PM
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