DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 37,768
NDA 21-008

Novartis Pharmaceuticals Corporation
Attention: Martha Propsner
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

WRITTEN REQUEST

Dear Ms. Propsner:

Reference is made to your Proposed Pediatric Study Request submitted to IND 37,768 on June 27, 2003, for Sandostatin (octreotide acetate) LAR Depot.

To obtain needed pediatric information on octreotide acetate, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

- ***Type of Study***: A randomized, double-blind, multicenter trial, for a minimum of 6 months duration, comparing 40 mg Sandostatin LAR Depot versus saline control in pediatric patients with hypothalamic obesity to evaluate efficacy, safety, and tolerability as a weight loss agent.

  Pharmacokinetic-Pharmacodynamic (PK-PD): 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 measurement (C_{trough}). Serum insulin concentrations must be measured at the same time points as octreotide concentrations are measured.

  Additional safety data from two previously conducted pediatric clinical studies using octreotide subcutaneous injections at 5 to15 ug/kg/day must also be submitted. This database will include safety information on pediatric patients with hypothalamic obesity receiving ≥ 12 months of octreotide therapy.

- ***Indication/Objective/rationale***:
  - To compare changes in body mass index (BMI) in pediatric patients with hypothalamic obesity treated with Sandostatin LAR Depot versus placebo.
  - To evaluate the safety and tolerability of Sandostatin LAR in pediatric patients with hypothalamic obesity.

- To compare baseline changes in waist-to-hip ratio, visceral and subcutaneous fat on quantitative CT, and weight in pediatric patients with hypothalamic obesity treated with Sandostatin LAR Depot versus placebo.
- To evaluate changes from baseline in dietary intake.
- To evaluate PK/PD relationship of Sandostatin LAR Depot in pediatric patients with hypothalamic obesity.

- ***Study Design*:** A randomized, double-blind, multicenter, safety and efficacy study in which pediatric patients with hypothalamic obesity will receive 40 mg octreotide or placebo monthly for a minimum of 6 months. Although the Agency will consider submission of the primary efficacy and standard safety data through month 6 as satisfying this Written Request, we remind you of your agreement to continue the study per the study protocol for an additional 6 months.

- ***Age group in which study will be performed:*** Male and female patients aged 6 through 17 years of age, inclusive. Efforts should be made to enroll a reasonable age distribution.

- ***Number of patients to be studied:*** 50 subjects randomized, 1:1, into placebo and 40 mg Sandostatin LAR treatment arms. Efforts should be made to enroll similar numbers of males and females.

- ***Entry Criteria***: Male and female patients with hypothalamic obesity who:
  - weigh greater than 120% of ideal body weight or have BMI greater than or equal to 27 **OR** have weight greater than 2 SD above the mean for age for at least one year after the last treatment for cranial disease.
  - have stabilized pituitary function tests. Those patients who have deficiencies in anterior pituitary hormone levels must have been on a stable replacement hormone regimen prior to study entry.

- ***Exclusion Criteria:***
  - Patients with severe cardiovascular dysfunction (cardiomyopathy)
  - Patients with severe neurological impairment that limits physical activity
  - Patients with a history of gallstones
  - Patients who have previously received octreotide
  - Patients who demonstrate poor tolerance of the test dose of subcutaneous octreotide
  - Patients currently under treatment with anti-neoplastic therapies
  - Patients who are post-menarcheal females not using an acceptable form of contraception
  - Patients with clinically active cardiac diseases, including valvulopathy

- ***Study endpoints:***

  Primary: BMI change from baseline at 6 months

  Secondary : - to compare changes in weight from baseline
  - changes in insulin and leptin from baseline

- changes in insulin, glucose, and triglycerides AUC at baseline following OGTT (oral glucose tolerance test)
- changes in waist-to-hip ratio from baseline
- change of intake of carbohydrates, fats, and protein
- change from baseline of visceral and subcutaneous fat
- proportion of patients who respond to study medication with change in BMI less than or equal to zero
- change in lean body mass as assessed by DEXA scan in patients who are not receiving growth hormone replacement therapy

PK-PD : 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.

- ***Drug Information***:

Dosage form: Sandostatin LAR Depot (octreotide acetate for injectable suspension) 20 mg
Route of Administration: IM (intragluteal)
Regimen: Arm A: Sandostatin LAR Depot, 40 mg each month for 6 months
Arm B: saline control, 2 cc injection each month for 6 months

- ***Drug-Specific Safety Concerns:***

- Effects on linear growth as monitored by stadiometry
- Effects on body composition as monitored by CT scan, waist-hip measurements
- Effects on progression to puberty as monitored by Tanner staging
- Effects on gallbladder function/formation of gallstones as monitored by routine ultrasonography
- Effects on nutrient absorption as monitored by Prothrombin Time (PT), routine blood chemistries, fecal fat measurements, serum carotene and homocysteine levels
- Effects on glucose dynamics as monitored by OGTT, HbA1c, fasting blood glucose, and plasma insulin levels
- Effects on cardiac parameters as monitored by routine echocardiograms, ECGs
- Effects on thyroid function as monitored by thyroid function tests

We note that you have agreed to establish a Data Safety Monitoring Board (DSMB) for all cardiovascular events.

- ***Statistical information, including power of study and statistical assessments:***
(Primary endpoint defined earlier in document.) The trial will test the null hypothesis that the mean changes from baseline in BMI at 6 months are equal in the two treatment groups versus the alternate hypothesis that the mean changes from baseline in BMI at 6 months are not equal. Testing will be performed at the 2-sided 5% significance level. Treatment groups

will be compared using contrasts in an analysis of covariance model (ANCOVA) with treatment as a factor and baseline BMI as covariate.
The intent-to-treat population, consisting of all randomized patients who take at least one dose of study medication, and have at least one post-baseline assessment, will be the primary analysis population. Missing 6-month data will be imputed using the last-observation-carried-forward (LOCF) method.
Summary statistics reported for the primary endpoint and all continuous secondary endpoints during baseline and treatment periods will include sample size, mean, median, standard deviation, minimum, and maximum.
Descriptive statistical summary of the primary PK parameters and PK/PD parameters will be presented.

- ***Labeling that may result from the studies*:** Appropriate sections of the label may be changed to incorporate the findings of the studies.

- ***Format of reports to be submitted*:** Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(s) must be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, or White. For ethnicity, one of the following designations must be used: Hispanic/Latino or Not Hispanic/Latino. Additional safety data from two previously conducted pediatric clinical studies using octreotide subcutaneous injections at 5 to 15 ug/kg/day must also be submitted. The reports from these trials will include safety information on pediatric patients with hypothalamic obesity receiving ≥ 12 months of octreotide therapy.

- ***Timeframe for submitting reports of the studies:*** Reports of the above studies must be submitted to the Agency on or before November 25, 2005. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

- ***Response to Written Request:*** As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request, then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted **as a supplement to NDA 21-008** with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to NDA 21-008. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Holly Wieland, Project Manager, at 301-827-6380.

Sincerely,

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Meyer
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