# MEDICAL OFFICER REVIEW

**Division of Metabolic and Endocrine Drug Products (HFD-510)**

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| **Application #:** 21-008 018 | **Application Type:** Pediatric Exclusivity and Labeling |
| **Sponsor:** Novartis | **Proprietary Name:** Sandostatin LAR® Depot |
| **Category:** Somatostatin analogue | **USAN Name:** Octreotide acetate for injectable suspension |
| **Indication:** Pediatric Hypothalamic Obesity | **Dose and Route of Administration:** IM injection, 40 mg per day |
| **Clinical Reviewer** Eileen Craig, MD | **Submission Date** 10 November 2005 |
| **BioPharmaceutics Reviewer** Wei Qiu, Ph.D. | **PDUFA Goal Date:** 10 May 2006 |
| **Statistical Reviewer:** J. Todd Sahlroot, Ph.D. | |

**Relevant IND** 37,768

**REVIEW SUMMARY:**

Please see Executive Summary

**OUTSTANDING ISSUES: None**

**RECOMMENDED REGULATORY ACTION:** N drive location:

XX Approve Not Approvable

Approvable

**SIGNATURES:** **Medical Reviewer:** Eileen Craig, MD **Date:** 2 May 2006

**Medical Team Leader:** Theresa Kehoe, MD **Date:**

# 1 EXECUTIVE SUMMARY

## 1.1 Recommendation on Regulatory Action

Approve requested labeling, with revisions. The sponsor is not seeking a new indication for Sandostatin LAR depot use in children.

## 1.2 Recommendation on Postmarketing Actions

None

## 1.3 Summary of Clinical Findings

Novartis has submitted this supplemental new drug application for Sandostatin LAR Depot (SAS-LAR, octreotide acetate for injectable suspension) seeking to fulfill the Pediatric Written Request and gain pediatric exclusivity. Sandostatin is an analogue of the natural hormone somatostatin. Secreted by multiple tissues including the hypothalamus and pancreas, somatostatin inhibits a variety of hormones including growth hormone, insulin, glucagon, cholecystokinin, secretin, gastrin and vasoactive intestinal peptide.

Study SMS995B 2403 was conducted in order to fulfill the Written Request to evaluate the efficacy, safety and tolerability of 40mg Sandostatin LAR Depot as a weight loss agent in pediatric patients with hypothalamic obesity. Hypothalamic obesity is thought to occur as a result of damage to the ventromedial nucleus of the hypothalamus. As a result, the brain can not appropriately process hormonal satiety signals and instead perceives a starvation state. The weight gain associated with hypothalamic obesity does not respond to traditional weight reduction methods or therapies. Prior small studies have shown some success using subcutaneous (sc) octreotide three times daily to decrease insulin secretion, decrease food intake, increase physical activity, and either stabilize weight gain or promote weight loss in pediatric patients with hypothalamic obesity. Therefore, it was hypothesized that SAS-LAR may be beneficial for weight control in the pediatric hypothalamic obesity population.

### 1.3.1 Brief Overview of Clinical Program

Study 2403 was a multicenter, double-blind, randomized, parallel-group, placebo-controlled study in children with hypothalamic obesity treated with 40mg of Sandostatin LAR® Depot or saline control administered as intramuscular injections monthly for 6 months.

In Study 2403, 62 patients were randomized into the study and 60 patients received study drug, had at least one post-baseline assessment and were included in the ITT and safety populations for analysis. Four patients in the safety population prematurely discontinued treatment (two in each treatment group) with two patients, one in each group, discontinued due to adverse events, after having received 4 months of treatment. The treatment groups were generally well balanced at baseline for demographic and disease characteristics. The mean age in this study was 13.6 years with a range of 6 to 17 years, inclusive. Twenty-five percent were < 12 years and 75% were ≥ 12 years of age. Within the < 12 year group: nine were on SAS-LAR and six were on placebo. Within the ≥ 12-year group: 21 were on SAS LAR and 24 were on placebo. All patients had a history of cranial insult, trauma or treatment of a cranial tumor, with subsequent abnormal weight gain faster than 2 standard deviations (SDs) above the mean for their age for at least one year leading to a diagnosis of hypothalamic obesity. The only relevant differences between treatment groups were in weight, where the saline control group were slightly heavier at baseline (89.0 kg vs. 81.7 kg in the SAS-LAR group), and for Tanner staging, where a slightly younger profile in the SAS-LAR group was evident.

The primary efficacy endpoint was change in BMI. The secondary efficacy endpoints included:

- Change from baseline in weight
- Change from baseline in waist to hip ratio
- Change from baseline in key biochemical and metabolic parameter, leptin (measured at screening, Month 3, and Month 6)
- Change from baseline in insulin dynamics (insulin, C-peptide, amylin and glucose) versus time profiles during the OGTT
- Change from baseline in body composition of fat, fat free mass (lean tissue) and bone based on DEXA scans and in visceral and subcutaneous fat in the abdomen by quantitative CT scan
- Change from baseline in volitional dietary intake, i.e. percent intake of carbohydrates, fats, and protein and physical activity
- Pharmacokinetic/Pharmacodynamic (PK/PD) relationships between octreotide concentration and insulin levels
- Pharmacokinetic (PK) parameters of SAS-LAR in pediatric patients
- Proportion of patients who show no increase in BMI ($\Delta$ BMI $\leq 0$)

After a screening period in which patients were administered a single injection of subcutaneous octreotide to check for tolerability, patients were randomized to receive SAS-LAR 40 mg/month or saline control by intragluteal injection monthly for 6 months.

Exposure to study medication was similar in the two treatment groups. The majority of patients received study medication for at least 120 days (4 months) and all these patients also completed the full course of injections administered at Months 0, 1, 2, 3, 4 and 5 in the double-blind treatment period. Overall, 43% of SAS-LAR-treated patients and 60% of control-treated patients received study medication for >150 days in Study 2403.

There was limited long-term drug exposure in the open-label extension study. Only three patients received 12 months of treatment. Only six out of 19 (32%) subjects who received placebo in Study 2403 and SAS-LAR in the OLE received study drug for 6 months.

### 1.3.2 Efficacy

The data presented do not demonstrate efficacy for use of SAS-LAR in pediatric patients aged 6 to <18 years with hypothalamic obesity. After 6 months of treatment with SAS-LAR or placebo, no difference in change from baseline in BMI was seen between treatment groups (0.1 kg/m$^2$ in the SAS-LAR-treated group vs. 0.0 kg/m$^2$ in the placebo-treated group, p=0.74). Mean weight gradually increased in both treatment groups from baseline to the end of the study (1.9 kg in the SAS-LAR-treated group vs. 1.8 kg in the placebo-treated group, p=0.93). The waist to hip ratio decreased in the SAS-LAR group whereas it increased in the control group (-0.014 in the SAS-LAR-treated group vs. +0.025 in the placebo-treated group, p=0.012). However, this isolated efficacy improvement is of questionable clinical relevance due to measurement imperfections. There was a statistically significant decline in insulin response and C-peptide AUC in favor of SAS-LAR treatment, but this did not correlate with a significant decrease in dietary intake. There was a trend toward a positive correlation (p=0.065) with physical activity scores in favor of SAS-LAR, while no correlation with changes in body fat was found.

Overall, Study 2403 failed to provide substantial evidence of effectiveness to support the use of SAS-LAR in the indication of pediatric hypothalamic obesity.

### 1.3.3 Safety

Adverse events that have been reported with Sandostatin LAR® Depot treatment in adults include gallbladder abnormalities (gallstones, sludge without stones, biliary duct dilatation), cardiac conduction abnormalities, and gastrointestinal symptoms (diarrhea, abdominal pain, flatulence, constipation, nausea, vomiting), hypoglycemia or hyperglycemia (due to alteration in the balance between the counter-regulatory hormones, insulin, glucagon and growth hormone), hypothyroidism, and depressed vitamin B12 levels (due to altered absorption of dietary fats). In Study 2403, a higher proportion of patients receiving SAS-LAR experienced AEs (SAS-LAR 93%, control 70%). The most frequent AEs during SAS-LAR treatment were diarrhea (SAS-LAR 37%, control 7%), cholelithiasis (SAS-LAR 33%, control 0%), and abdominal pain (SAS-LAR 13%, control 3%), while nasopharyngitis occurred with similar frequency in both arms (SAS-LAR 30%, control 27%).

Eleven patients (11/30, 37%) were found to have new or worsened abnormalities of the gallbladder by the end of Study 2403. All cases involving gallstones (10 patients) were reported in the SAS-LAR group. Nine cases were asymptomatic and were detected by ultrasound at the end of the study. One of these patients developed severe gallstones associated with pancreatitis about 3 months after the last dose of study drug. In Study 2403, there were no cardiac conduction abnormalities reported. There was one case (1/30, 3%) of pericardial effusion in the SAS-LAR treatment group. The incidence of gastrointestinal disorders was 47% for the SAS-LAR group and 20% for the placebo group, with diarrhea (37% SAS-LAR, 7% placebo) and abdominal pain (13% SAS-LAR, 3% placebo) as the most common symptoms.

There were no episodes of hypoglycemia reported in the study. Three subjects (10%) in the SAS-LAR group and 2 subjects (7%) in the placebo group developed impaired glucose tolerance. One subject (3%) in the SAS-LAR group was diagnosed with diabetes mellitus during the study. Two subjects, both in the SAS-LAR group, developed abnormalities in thyroid function tests – one with a suppressed thyroid stimulating hormone level and one with a decrease in free thyroxine. There was no evidence of decrease vitamin B12 levels or increased methylmalonic acid levels with SAS-LAR therapy.

The sponsor initiated, but did not complete, the 6-month open-label extension study (OLE). It was the unanimous recommendation of the Data Safety Monitoring Board that the OLE be terminated as soon as possible due to the lack of efficacy and the high risk of gallstone formation. All subjects received SAS-LAR in the OLE with subjects receiving SAS-LAR for both core and extension phases of the study identified as the C + E group and subjects receiving placebo in the core phase and SAS-LAR in the OLE phase identified as the SAS-LAR OLE group. A total of 32 subjects participated in the OLE (13 in the C + E group and 19 in the SAS-LAR OLE group) with 9 (28%) subjects completing the full 6 month extension phase (3 in the C + E group and 6 in the SAS-LAR OLE group). Serious adverse events (SAEs) were reported for nine (28%) patients [three (23%) in the C+E group and six (32%) in the SAS-LAR OLE group]. Four of the nine (44%) SAEs were related to cholelithiasis, three (33%) to biliary tract abnormalities, and two (22%) to gastrointestinal disorders. Eleven patients (34%) were found to have new or worsened abnormalities of the gallbladder by the end of the extension study.

The safety profile of SMS-LAR in pediatric patients was consistent with the known safety profile of sandostatin as seen in adults in other indications. The incidence of diarrhea in clinical trials of adult patients with acromegaly is 36%, which is similar to the incidence of 37% seen in this trial. The incidence of abdominal pain or discomfort in clinical trials of adult patients with acromegaly is 29%, which is higher than the incidence of 17% for abdominal pain and upper abdominal pain seen in this trial. However, the incidence of new cholelithiasis in this pediatric population (33%) was higher than that seen in other adult indications such as acromegaly (22%) or malignant carcinoid syndrome (24%).

### 1.3.4 Dosing Regimen and Administration

The dose selected for use in Study 2403 was primarily based on data from the two previously conducted pediatric studies. Sandostatin LAR® Depot was given as two 20 mg intragluteal injections per month for a total dose of 40mg/month for 6 months.

### 1.3.5 Drug-Drug Interactions

Not applicable in this submission.

### 1.3.6 Special Populations

The study was performed in a pediatric population between the ages of 6 and 17, inclusive.

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Mary Parks

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