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Subject: Update on Pediatric Postmarketing Adverse Events  
Drug Name(s), NDA: Sandostatin LAR (octreotide), NDA 021008  
Pediatric Exclusivity  
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## **EXECUTIVE SUMMARY**

This document updates a previous (March 2007) OSE review<sup>1</sup> of pediatric post-marketing adverse event reports associated with octreotide (Sandostatin Injection, Sandostatin LAR Depot). The review, presented at the April 11, 2007 Pediatric Advisory Committee (PAC) meeting, indicated FDA had received 52 pediatric octreotide reports (including 11 deaths) since initial marketing in 1988 through February 12, 2007. The PAC members requested a one-year update on octreotide adverse event reports, with focus on necrotizing enterocolitis, hypoxia, and deaths.<sup>5</sup>

Since the 2007 review, between February 12, 2007 and May 22, 2008, AERS received ten new pediatric adverse event reports associated with octreotide. These include one report of necrotizing enterocolitis that involved a 2-month-old male with refractory chylothorax and congenital heart disease. There were no reports of hypoxia. There was one report of death, involving a newborn with microcephaly and other conditions who was started on octreotide for insulinoma and died from unknown causes about a month later. Similar to findings in the previous review, management of chylothorax and hyperinsulinism were frequently reported reasons for octreotide use; most of the reports were associated with Sandostatin Injection; at least half of the reports involved children less than two years of age; and there was a wide range of reported octreotide doses.

It is challenging to place these octreotide reports in the context of usage given the underreporting of pediatric adverse event events<sup>6,7</sup> and difficulty in assessing the reason for octreotide use and extent of exposure in the overall pediatric population. Further, it is not known how weight-based dosing, duration of therapy, or underlying conditions might impact response to octreotide when used in pediatrics, particularly in children less than two years of age. Since octreotide is only approved for adult indications, all pediatric use is off-label. The Sandostatin Injection labeling contains a lengthy description of 49 published pediatric case reports. The usefulness of this description is unknown, but may mislead clinicians to assume octreotide has been proven to be safe and effective for pediatric use.

In conclusion, FDA continues to receive serious adverse event reports associated with octreotide off-label use in pediatrics. It seems reasonable that AERS post-marketing experience be communicated to healthcare providers, and studies be undertaken to further evaluate the safe use of octreotide in the pediatric population, including infants and neonates. OSE recommends:

- 1) Communicate to health care professionals that FDA has received serious adverse events associated with octreotide use in pediatrics.
- 2) Engage the sponsor and or clinical community to investigate pediatric uses of octreotide and facilitate the reporting of pediatric octreotide adverse events.
- 3) Revise the labelings to clarify there are no approved pediatric indications, and remove the description of the 49 published case reports from the Sandostatin Injection labeling.

## **1 INTRODUCTION**

This document updates a 2007 Office of Surveillance and Epidemiology (OSE) post-marketing review<sup>1</sup> of pediatric adverse events associated with octreotide (Sandostatin, Sandostatin LAR Depot). The 2007 review was performed under the Best Pharmaceuticals for Children Act (BPCA), which mandates the review of post-marketing adverse event reports during the one-year period after a drug receives an additional six-months of market exclusivity. The review revealed FDA had received 52 pediatric octreotide cases (including 11 deaths) since initial marketing in 1988 through February 12, 2007. Nearly all (n=49/52) of the cases were associated with Sandostatin Injection, and about half (n=24/52) of the cases involved children less than two years of age. Reported pediatric doses and routes of administration varied widely. Pediatric off-label use was readily described in the literature.<sup>2,3</sup> Further, the Pediatric Use section of both the Sandostatin Injection and Sandostatin LAR Depot labelings described off-label uses and associated doses,<sup>4</sup> which may have lead to confusion that octreotide is approved for certain uses in children. The review recommended 1) communicating post-marketing adverse event findings to healthcare providers, 2) revising the Sandostatin Injection and Sandostatin LAR Depot labelings to improve consistency between the labelings, as well as clarifying there are no approved pediatric indications for octreotide, and 3) engaging the sponsor to investigate pediatric uses of octreotide.

### **1.1 Reason for Review**

Octreotide was presented at the Pediatric Advisory Committee (PAC) meeting on April 11, 2007. At that meeting, the PAC members recommended a one-year update on post-marketing adverse events associated with octreotide, with particular focus on necrotizing enterocolitis (NEC), hypoxia, and deaths.<sup>5</sup> The slides, briefing materials and transcript for the April 11, 2007 meeting can be found at <http://www.fda.gov/ohrms/dockets/ac/oc07.htm>.

## 2 METHODS AND MATERIALS

### 2.1 Selection of AERS Cases

Using the search criteria described below, the Adverse Event Reporting System (AERS) was searched in May 2008 for octreotide reports. The reports identified from the search were downloaded and individually reviewed.

Search Criteria	
<i>Query Date:</i>	22May2008
<i>Product:</i>	Octreotide (ingredient, trade, and verbatim search)
<i>Search Terms:</i>	All
<i>Search Dates:</i>	12Feb2007* through 22May2008
<i>Countries:</i>	All (foreign and domestic)
<i>Ages:</i>	All (categorized by age: pediatric, < 17 years; adults, ≥ 17 years)
<i>Combination Products:</i>	No
<i>Concomitant Products:</i>	No
<i>Outcome:</i>	All
<i>Exclusion Criteria:</i>	Reports described in previous OSE review

\*Cutoff date for previous 2007 OSE review<sup>1</sup>

## 3 RESULTS

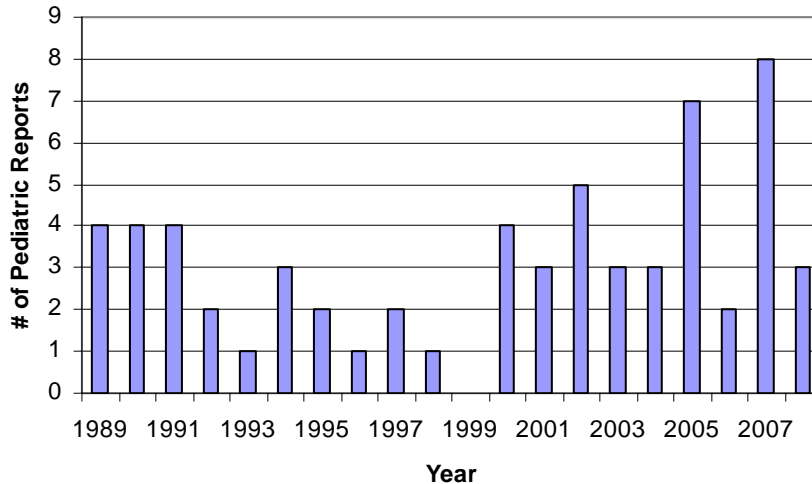
### 3.1 AERS Crude Counts

As presented in Table 1 below, AERS contains 10 pediatric cases that were received since the previous 2007 OSE review. None of the 10 cases are from the United States.

<b>Table 1: Crude counts of Octreotide Reports</b> (US counts in parentheses)			
Source: AERS, Reports Received Between 12Feb2007 (cutoff date for previous OSE review) and May 22, 2008			
	All reports (US)	Serious* (US)	Death (US)
Adults (≥ 17 yrs.)	123 (44)	119 (43)	17 (5)
Pediatrics (0-16 yrs.)	10 (0)	10 (0)	1 (0)
Age unknown (Null values)	50 (14)	49 (13)	8 (1)
Total	183 (58)	178 (56)	25 (6)
*Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, and congenital anomaly.			

### 3.2 Reporting Trend for Pediatric Octreotide Reports in AERS

**Figure 1. Total (Non-Duplicated, Serious and Nonserious) Number of Pediatric Octreotide Reports in AERS (n=62), By Year (Marketing Through Cut-off Date of May 22, 2008).**



### 3.3 AERS Case Characteristics

Characteristics of the 10 pediatric cases are presented in Table 2 below, and a summary of the 10 cases is provided in APPENDIX I. There was one report (ISR 5730096) with limited information of two episodes of necrotizing enterocolitis (NEC) that occurred in a newborn, with history of premature birth (birth weight, 1.5 kg), congenital heart disease and refractory chylothorax. The child received three courses of octreotide, “one course noted concurrent NEC.” The “third course also coincided with NEC.” The physician reporter indicated the episodes started within 48 hours of starting octreotide. There was one report of death, that involved a newborn with microcephaly, retromicrognathia, hypertelorism, and hypotonia, who started octreotide 30 mcg every 8 hours subcutaneously for insulinoma and died about a month later (cause of death unknown). Like the previous 2007 OSE review, management of chylothorax and hyperinsulinism are frequently reported reasons for use in the pediatric population. Also, like the previous review, most of the reports are associated with Sandostatin Injection versus Sandostatin LAR Depot. There is a male predominance, and at least half of the reports involve children less than two years of age. There is also a wide range of reported doses.

<b>Table 2. Characteristics of Pediatric Octreotide Cases (n=10).</b> Source: AERS, Reports Received Between 12Feb2007 (cutoff date for previous OSE review) and May 22, 2008		
<b>Characteristic</b>	<b>Total Reports (% of 10 reports)</b>	
<b>Number of U.S. Reports</b>	0 (0%)	
<b>Gender</b>		
Male	7 (70%)	
Female	1 (10%)	
Unknown Gender	2 (20%)	
<b>Age</b>		
< 2 years:	5 (50%)	
Median: 3 months	2-5 years:	1 (10%)
Average: 4.1 yrs (Standard Deviation: 6)	6-11 years:	0 (0%)
Range: newborn to 16 yrs	12-16 years:	2 (20%)
	Unknown Age:	2 (20%)
<b>Dose (by route of administration)</b>		
Subcutaneous	2-300 mcg daily (n=3)	
Intravenous, infusion	0.5-10 mcg/kg/hr (n=2)	
Intravenous, other	5 mcg/kg/day (n=1)	
Intramuscular (Sandostatin LAR)	20 mg (n=1)	
Other (in utero exposure)	Maternal dose: 10-30 mg monthly (n=1)	
Unknown	(n=2)	
<b>Exposure Time To Event (Or Duration of Therapy if Exposure Time Not Reported)</b>		
< 2.5 months	6 (60%)	
In utero exposure	1 (10%)	
Unknown exposure time	3 (30%)	
<b>Reason for Octreotide Use</b>		
Chylothorax	4 (40%)	
Hypoglycemia/Hyperinsulinism	2 (20%)	
Insulinoma	1 (10%)	
Pituitary Adenoma/Gigantism	1 (10%)	
Diarrhea	1 (10%)	
In utero exposure	1 (10%)	

**Table 2. Characteristics of Pediatric Octreotide Cases (n=10).** Source: AERS, Reports Received Between 12Feb2007 (cutoff date for previous OSE review) and May 22, 2008

Characteristic	Total Reports (% of 10 reports)
<b>Reported Adverse Events†</b>	
Bradycardia	2
Cardiac arrest, transient	1
Death	1
Hypoadrenalism	1
Hypoglycemia	1
Hyperglycemia	1
Hypotension	1
Metabolic acidosis and fluid retention	1
Necrotizing enterocolitis and bloody stools	1
Osteonecrosis, femoral head	1
Persistent effusion (loss of efficacy)	1

†Numbers may not sum due to reports describing more than one adverse event

## 4 DISCUSSION

FDA continues to receive adverse event reports associated with octreotide use in pediatrics. It is challenging to place these reports in the context of usage given the underreporting of pediatric adverse event events<sup>6,7</sup> and difficulty in assessing the reason for use (with associated patient age and doses) and extent of exposure in the overall pediatric population.<sup>8</sup> Yet, we cannot dismiss these reports. First, many of the pediatric octreotide reports received by FDA since initial marketing in 1988 are of a serious nature. Second, despite the uncertainty of a causal relationship between the adverse event and octreotide or an underlying medical condition, nearly all of the reports are from attending medical specialists. Third, the off-label use of octreotide in the pediatric population is continually described in published literature. For example, since the previous 2007 OSE review, a MEDLINE search identified two published pediatric case reports (one describing use of octreotide for pleural effusions<sup>9</sup> and the other describing management of symptoms associated with malignant bowel obstruction<sup>10</sup>) along with a review describing the use of octreotide for the prevention of hypoglycemia in patients with sulfonylurea overdose.<sup>11</sup> Lastly, octreotide is indicated for the management of conditions that typically only occur in adults (acromegaly, carcinoid tumors, and vasoactive intestinal peptide tumors), and octreotide has not been widely studied in the pediatric population.<sup>12</sup> Thus, it is not known how weight-based dosing, duration of therapy, or underlying conditions might impact the pharmacokinetic and pharmacodynamic properties of octreotide when used in a pediatric setting, particularly in children less than two years of age. Octreotide, as a somatostatin analog, has a multitude of pharmacologic



effects that include inhibiting growth hormone, glucagon, insulin, and gallbladder contractility; decreasing splanchnic blood flow; and suppressing secretion of thyroid stimulating hormone, and release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.

In the previous review, OSE recommended revisions to both the Sandostatin and Sandostatin LAR Depot labelings to improve consistency and clarify there are no approved pediatric indications for octreotide. In March 2008, the Pediatric Use section of the Sandostatin LAR Depot labeling was revised to 1) include the results of the pediatric study on hypothalamic obesity and 2) remove discussion on the use of Sandostatin Injection for congenital hyperinsulinism. However, the description of 49 published pediatric case reports remains in the Sandostatin Injection labeling (see APPENDIX II). The usefulness of this lengthy description is unknown. The description includes statements that may mislead clinicians to assume octreotide has been proven safe and effective for pediatrics, and approved for pediatric indications. For example, despite the lack of supporting efficacy data, the Pediatric Use section states, “octreotide is an alternative medical treatment to diazoxide...” Furthermore, the source of the reports and time frame is not provided so it is unknown if any of the 49 pediatric reports are from studies, or when the section was last updated.

It isn't clear why FDA did not receive any US reports during the time period (February 12, 2007 through May 7, 2008) for this review. The previous 2007 review found 63 percent (n=33/52) of the reports were from the United States. FDA is aware of significant underreporting of pediatric adverse events,<sup>6,7</sup> but it is also possible pediatric off-label use in the United States has decreased. However, at the April 11, 2007 PAC meeting, members felt octreotide use is increasing, particularly in at-risk children.<sup>5</sup> The PAC members also suggested modifying the labeling or alerting practitioners that FDA has received these adverse event reports associated with octreotide use in children who may be susceptible to the effects of octreotide. However, at the present time, OSE cannot make specific recommendations regarding the addition of pediatric post-marketing experience to the octreotide labelings without study data (particularly in children less than two years of age).

## 5 CONCLUSION

FDA continues to receive serious adverse event reports associated with octreotide off-label use in pediatrics. It seems reasonable that AERS post-marketing experience be communicated to healthcare providers, and studies be undertaken to further evaluate the safe use of octreotide in the pediatric population, including infants and neonates. As suggested previously<sup>1</sup>, OSE recommends:

- 1) Communicate to health care professionals that FDA has received serious adverse events (including deaths) associated with octreotide use in pediatrics. This communication could be via through the FDA (e.g., Drug Safety Newsletter) or a pediatric-specialty journal.
- 2) Engage the sponsor and or pediatric/neonatology practitioner community to:

- a. Perform a thorough and systematic review to see what pharmacokinetic, efficacy, and safety information for different pediatric uses are available as a background to identify areas of needed clinical research
  - b. Investigate pediatric uses of octreotide (identified above as areas of needed clinical research) in controlled settings.
  - c. Initiate an educational campaign targeted toward specialty areas such as neonatology and pediatrics, notifying prescribers of reported adverse events associated with octreotide use in the pediatric population, and encouraging prescribers and hospitals to report adverse events associated with octreotide in the pediatric population.
- 3) Revise the Sandostatin Injection and Sandostatin LAR Depot labelings:
- a. Clarify in the Pediatric Use section, there are no approved pediatric indications.
  - b. Remove the description of the 49 published pediatric case reports from the Sandostatin Injection Pediatric Use section of the labeling.

## 6 APPENDICES

### Appendix I. Summary of Pediatric Octreotide Cases in AERS (Received by FDA February 12, 2007 Through Cut Off Date, May 22, 2008).

ISR # Source	Age Weight Sex	Use	Dose	Adverse Event	Time to Event	Description:
5265979 NE	4 yo 20 kg Male	Chylothorax	---	Hypotension	1 dy	4-year-old boy experienced hypotension one day after receiving octreotide (dose unknown) for chylothorax. Octreotide dose decreased.
5400190 JP	1 dy 3 kg Female	In utero exposure	Mother: 30 mg mo IM	Hypoglycemia	~8 mo exposure	Literature report of in utero exposure to octreotide. 37-year-old mother with acromegaly treated with SAS-LAR 30 mg/month (discontinued at 4 months gestation, but restarted). Newborn (3.1 kg weight; Apgar 9 at one minute and 10 at five minutes) developed transient hypoglycemia (glucose level: 40 mg/dL at birth, 28 mg/dL at one hour). Treated with glucose; child recovered.
5474578 JP	12 yr --- Male	Pituitary adenoma/ Gigantism	20 mg IM	Osteonecrosis, femoral head	2.5 mo	12-year-old boy experienced femoral head osteonecrosis while on treatment with SAS-LAR 20 mg. The boy had "slipped femoral epiphysis in the left and opposite side and had received pinning in bilateral sides. MRI showed retention of articular fluid in right side, suggesting inflammation."
5481234 IN	3 mo 4 kg Male	Hyperinsulinism	0.5 mcg q6hr SC	Hyperglycemia/ Bradycardia	Unk	Literature report of a 3-month old male with congenital hyperinsulinism (glucose level: 40-50 mg/dL) on octreotide 0.5 mcg every 6 hr SC underwent subtotal pancreatectomy. After induction, blood glucose was 160 mg/dL, and after 15 minutes, 348 mg/dL. 20 minutes post-induction, heart rate decreased to 35 BPM. Blood glucose remained consistently high, and increasing the insulin dose 10-fold was of no benefit. Following surgery, the insulin was tapered as blood sugar normalized. The rest of the child's hospitalization was uneventful.

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**Appendix I. Summary of Pediatric Octreotide Cases in AERS (Received by FDA February 12, 2007 Through Cut Off Date, May 22, 2008).**

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ISR # Source	Age Weight Sex	Use	Dose	Adverse Event	Time to Event	Description:
5557967 JP	Newbn 1.9 kg Male	Hyperinsulinism	5 mcg/kg/d IV	Hypoadrenalism	Unk	Literature report of a newborn (1.9 kg weight) who experienced hypoglycemia after birth. Treated initially with glucose and hydrocortisone. Later diagnosed with persistent hyperinsulinemic hypoglycemia of infancy; diazoxide 20 mg/kg and octreotide 5 mcg/kg/day were added. When hydrocortisone dose was decreased to 4 mg/day, the child experienced respiratory insufficiency, adrenal insufficiency, and central hypothyroidism. Authors concluded "it is not clear whether hypoadrenalism was induced by octreotide or existed as an underlying disease." Octreotide and diazoxide were discontinued; events resolved.
5587191 BZ	1 mo --- Male	Insulinoma	30 mcg every 8 hrs SC	Death	1 mo	Newborn with multiple complications (microcephaly, retromicrognathia, hypertelorism, hypotonia, and mild tachypnea) started octreotide for insulinoma. The child died about a month later. No further information provided.
5386222 GE	--- --- ---	Chylothorax	0.5 to 4 mcg/kg/hr	Metabolic acidosis and fluid retention	Unk	A child (unknown age) experienced metabolic acidosis and fluid retention an unknown time after starting octreotide 0.5 - 4 mcg/kg/hr. Outcome unknown.
5657378 TU	Newbn 3 kg Male	Chylothorax	1-10 mcg/kg/hr	Persistent effusion (loss of efficacy)	1 mo	Literature report of a male newborn (3 kg weight) who experienced bilateral pleural effusion. Octreotide started and increased to 10 mcg/kg/hr. Clinical status improved with cessation of drainage on day 28. Octreotide dose decreased and infant was extubated. However, on day four post-extubation, the child developed respiratory distress with reaccumulation of persistent drainage. Surgical pleurodesis performed. Child improved and was discharged.

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**Appendix I. Summary of Pediatric Octreotide Cases in AERS (Received by FDA February 12, 2007 Through Cut Off Date, May 22, 2008).**

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ISR # Source	Age Weight Sex	Use	Dose	Adverse Event	Time to Event	Description:
5730096 UK	2 mo --- Male	Chylothorax	10 mcg NOS	Bloody stools, necrotizing enterocolitis	48 hrs	2-month-old male, with history of premature birth (birth weight, 1.5 kg), congenital heart disease and refractory chylothorax (treated with medium chain triglycerides, parenteral nutrition) received three courses of octreotide. "One course noted concurrent NEC," and the "third course [10 mcg octreotide] also coincided with NEC." The "episode starting usually within 48 hours of starting octreotide." No additional information available.
5734622 JP	16 yr --- ---	Diarrhea	300 mcg/d cont SC infusion	Bradycardia and "transient" cardiac arrest	7 d	Patient with AML started octreotide 300 mcg/day continuous SC infusion for diarrhea due to graft-versus-host disease following transplant. Seven days later, the patient experienced bradycardia, "sinus failure" and "transient cardiac arrest." The patient was also receiving an unspecified medicine to "raise pulse rate." Patient recovered.

SAS-LAR=Sandostatin LAR Depot

## **APPENDIX II: Pediatric Use Sections of the most recent labeling versions of the Sandostatin LAR Depot and Sandostatin Injection**

### **Sandostatin LAR Depot (March 2008 version)**

#### **8.4 Pediatric Use**

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 ng/ml. Steady-state concentration was achieved after 3 injections of a 40 mg dose.

The efficacy and safety of Sandostatin LAR Depot were examined in a randomized, double-blind, placebo controlled six month study in 60 pediatric patients aged 6-17 years with hypothalamic obesity resulting from cranial insult. Mean BMI increased 0.1 kg/m<sup>2</sup> in Sandostatin LAR Depot-treated subjects compared to 0.0 kg/m<sup>2</sup> in saline control-treated subjects. Diarrhea occurred in 11 of 30 (37%) patients treated with Sandostatin LAR Depot. No unexpected adverse events were observed. However, with Sandostatin LAR Depot 40 mg once a month, the incidence of new cholelithiasis in this pediatric population (33%) was higher than that seen in other adults indications such as acromegaly (22%) or malignant carcinoid syndrome (24%), where Sandostatin LAR Depot was 10 to 30 mg once a month.

### **Sandostatin Injection (September 2005 version)**

#### **Pediatric Use**

Experience with Sandostatin® (octreotide acetate) in the pediatric population is limited. Although formal controlled clinical trials have not been performed to evaluate safety and effectiveness in this age group, there are reports of 49 cases in the literature of neonates and infants with congenital hyperinsulinism [also called familial hyperinsulinism (HI), persistent hyperinsulinemic hypoglycemia of infancy (PHHI), or nesidioblastosis] who have received Sandostatin® as an inhibitor of insulin release. The following efficacy and safety information is derived from these 49 patients.

Sandostatin® has been used to stabilize plasma glucose levels prior to pancreatectomy and to treat recurrent post-operative hypoglycemia. Although most use of octreotide in this setting is short-term, a few reports in the literature have documented longer-term therapy in pediatric patients (2.2-5.5 years). Octreotide is an alternative medical treatment to diazoxide for control of hypoglycemia in this disorder. Of 31 pediatric patients who received Sandostatin® as prescribed for congenital hyperinsulinism and for which long-term follow-up was available, octreotide obviated the need for surgery in 3 patients (10%) and was replaced by diazoxide in 4 patients (13%) due to uncontrolled hypoglycemia. Although the remainder of these patients required surgery, there have been a few reports in the literature of patients who have responded to octreotide after failing treatment with surgery and/or diazoxide. Doses of 3-40 mcg/kg/day have been used. At these doses, the majority of side effects were gastrointestinal: diarrhea, steatorrhea, vomiting, and abdominal distention, each reported in 22%-35% (n = 11-17) of patients. However, they were generally short-lived – with resolution of vomiting and distention in 2-4 days, and diarrhea/steatorrhea, within 2-4 weeks. Steatorrhea was controlled in most patients with pancreatic enzyme supplements. Poor growth was reported in 37% of patients (n = 7) who received Sandostatin® for 1-4.33 years. It was associated with low serum growth hormone and/or IGF-1 levels in 4/6 patients in whom these parameters were measured. Catch-up growth occurred in 3/3 patients who were followed after

Sandostatin® was discontinued. Poor weight gain was reported in 32% of patients (n = 6). Tachyphylaxis was reported in 35% (n = 17) of patients. Asymptomatic gallstones with sludge was reported in one infant after one year of therapy and was treated with ursodeoxycholic acid. There has been a single report of an infant with nesidioblastosis who experienced a seizure thought to be independent of Sandostatin® therapy. A single death has been reported in a 16-month-old male with enterocutaneous fistula who developed sudden abdominal pain and increased nasogastric drainage and expired 8 hours after receiving a single 100 mcg subcutaneous dose of Sandostatin.

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