MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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SUBJECT: Post-Pediatric Exclusivity Postmarketing Adverse Event Review
Drug: Octreotide (Sandostatin LAR Depot [NDA 21-008])
Pediatric Exclusivity Approval Date: January 12, 2006

RCM # 2007-50

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1. EXECUTIVE SUMMARY

This document summarizes octreotide acetate (Sandostatin LAR Depot and Sandostatin) pediatric adverse event reports in the FDA's Adverse Event Reporting System (AERS). Although pediatric exclusivity was granted for Sandostatin LAR Depot (the long-acting dosage form of octreotide administered intragluteal on a monthly basis), the Office of Pediatric Therapeutics (OPT) and the Pediatric and Maternal Health Staff (PMHS) requested the Division of Drug Risk Evaluation (DDRE) review all octreotide reports (including Sandostatin Injection, which is administered subcutaneously or intravenously) associated with pediatric use. Up to the AERS cut-off date of February 12, 2007, AERS contained 1,279 cases for octreotide (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately four percent of the total octreotide reports in AERS (52/1,279).

During the one-year period following the approval of pediatric exclusivity for Sandostatin LAR Depot on January 12, 2006, FDA received one pediatric adverse event report involving Sandostatin LAR Depot – a 20-day-old male with congenital nesidioblastoma who experienced "tachycardia, edema, fever, and vasodilation" 12 hours after receiving 6 mg of Sandostatin LAR Depot. During this one-year period, FDA also received one pediatric report involving Sandostatin Injection – a premature infant with history of Noonan syndrome and congenital chylothorax who developed abdominal distention two weeks after starting octreotide. The child died at 4-months of age, due to "hypoglycemia, anuria, pneumothorax and cardiac arrest."

Since U.S. marketing approval of octreotide (Sandostatin Injection in 1988 and Sandostatin LAR Depot in 1998), FDA received 52 pediatric adverse event reports (including the two reports described above during the one-year period following the date pediatric exclusivity was granted for Sandostatin LAR Depot). Ninety-four percent of the reports are associated with Sandostatin Injection, and about half (n=24) of the 52 reports occurred in children less than two years of age. All of the pediatric octreotide use is considered off-label, as there are no approved pediatric indications. Off-label use of octreotide is promoted in the literature, and parallels the reported indications for use in the pediatric adverse event reports. Furthermore, the Pediatric Use sections of the Sandostatin LAR Depot and Sandostatin labelings describe off-label use (and associated doses) and some may misinterpret octreotide as being approved for certain uses in children. Reported doses varied widely. For example, in children less than 2 years of age, the median reported dose was 12 mcg/kg/day, but doses ranged from 0.6 to 432 mcg/kg/day. Continuous infusion of octreotide in pediatric patients was reported. However, continuous infusion of octreotide has not been studied, and is not an approved method of administration in any population for any indication.

This review identified serious adverse events (including 11 deaths) associated with octreotide use in pediatrics (which is all off-label use). Seven of the eleven deaths were reported in children less than two years of age. The top four System Organ Classes (SOCs) associated with the reported pediatric octreotide adverse events are: Gastrointestinal Disorders (n=14), General Disorders and Administration Site Conditions (n=14), Respiratory Disorders (n=13), and Cardiac Disorders (n=11). Reported adverse events identified as unlabeled are mainly associated with Respiratory Disorders (n=7) and Gastrointestinal Disorders SOCs (n=5), but

were seen in numerous SOCs. However, comparing labeled and unlabeled adverse events has limited usefulness because the population studied for approval of octreotide (such as acromegalics) often have underlying disease or are at increased risk of certain diseases because of the treatment they receive. This review did not confirm the presence of similar adverse events associated with octreotide use in the adult population. However, some of the pediatric adverse event reports like necrotizing enterocolitis do not typically occur in adults, and a comprehensive review of the adult octreotide adverse event reports in AERS is required to further investigate an association. See Section 5 for more information on the reported pediatric adverse events.

It is possible octreotide directly causes the reported adverse events such as hypoxia, cardiac dysfunction, hepatic failure, and necrotizing enterocolitis in the pediatric population. Octreotide, a somatostatin analog, is pleiotropic with many inhibitory effects. There is a potential temporal relationship since 27 percent reported the adverse event occurred within 24 hours of starting octreotide. There are also reports of rechallenge – pediatric patients who reexperienced hypoxia with subsequent doses of octreotide. However, it is not clear how high doses, duration of therapy, or underlying conditions in the pediatric population (such as prematurity) might impact the pharmacokinetic and pharmacodynamics of octreotide. One published article questioning the safety of octreotide in neonates, recommends octreotide be "limited to patients with stable hemodynamic findings without recent history of compromised splanchnic perfusion."[7]

Based on the findings of this review of pediatric adverse event reports in AERS, DDRE recommends:

1) Communicate to health care professionals that FDA has received serious adverse events (including deaths) associated with octreotide use in pediatrics. This could be done in accordance with the FDA's guidance on communicating drug safety to the public[20] and/or brief report in a pediatric journal.

2) Revise the Pediatric Use sections in both the Sandostatin LAR Depot and Sandostatin labelings to:

    a. Clearly note there are no currently approved pediatric indications for octreotide.
    b. Provide consistent wording to both package inserts.
    c. Provide post-marketing updated adverse event information.

3) Engage the sponsor to:

    a. Initiate an educational campaign targeted toward specialty areas such as neonatology and pediatrics, instructing the prescribers regarding the reported adverse events associated with octreotide use in the pediatric population.
    b. 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
    c. Investigate pediatric uses of octreotide (identified above as areas of needed clinical research) in controlled settings. Clinicians or investigators willing to investigate octreotide use in the pediatric population could contact the sponsor. The sponsor already has a website for clinical trial information on their products and provides a

contact number for more information on their clinical trials with Sandostatin LAR Depot.

In a separate document, DDRE will review adult octreotide adverse event reports in AERS and make recommendations about revising both the Sandostatin LAR Depot and Sandostatin labelings.

2. INTRODUCTION

This document summarizes octreotide acetate (Sandostatin LAR Depot and Sandostatin) pediatric adverse event reports in the FDA's Adverse Event Reporting System (AERS). The Office of Pediatric Therapeutics (OPT) and Pediatric and Maternal Health Staff (PMHS) requested this information in preparation for their Pediatric Advisory Committee (PAC) meeting scheduled for April 11, 2007. Although FDA granted Pediatric Exclusivity for Sandostatin LAR Depot (SAS-LAR), which is the long-acting dosage form of octreotide administered intragluteal every four weeks, OPT and PMHS requested Division of Drug Risk Evaluation (DDRE) also review pediatric reports associated with Sandostatin Injection (SAS), which is administered subcutaneously or intravenously.

Preliminary review of octreotide by PMHS indicate, during the one-year period following the date pediatric exclusivity was granted for Sandostatin LAR Depot, FDA received a pediatric octreotide report of pneumothorax, abdominal distention, hypoglycemia, with subsequent death due to cardiac arrest associated with oliguria and anuria. Prior to the granting of pediatric exclusivity, the PMHS identified pediatric octreotide reports with the following unlabeled serious adverse events: hypoxia, necrotizing enterocolitis, cataracts, hyponatremia, premature birth after intrauterine exposure, and drug dependence/drug intolerance. Therefore, OPT and PMHS requested DDRE review all reports associated with octreotide with particular focus on unlabeled serious adverse events.

3. PRODUCTS, INDICATIONS, PEDIATRIC LABELING, AND PEDIATRIC FILING HISTORY

3.1. Octreotide Products Available in the United States (Table 1)

Table 1. Description of Octreotide Products Available in the United States.
Source: 9/2/2005 (Sandostatin) and 5/10/2006 (Sandostatin LAR) Approved Labeling[1]

Product Description	NDA	Approval Date	Route/Administration	Available Strengths
Octreotide (Sandostatin Injection [SAS])				
	19-667	10/21/1988	Subcutaneous or intravenously 2-4 times per day	*Ampules* (1 mL): 50 mcg/mL, 100 mcg/mL, 500 mcg/mL *Multi-dose vials* (5 mL): 200 mcg/mL, 1000 mcg/mL
Octreotide (Sandostatin LAR Depot [SAS-LAR]) (long-acting dosage form of microspheres [biodegradable glucose star polymer] containing octreotide)				
	21-008	11/25/1998	Intragluteal injection every 4 weeks	*Kits*: 10 mg, 20 mg, 30 mg

3.2 Octreotide Approved Indications (Table 2)

Table 2. Octreotide Approved Indications.
Source: 9/2/2005 (Sandostatin) and 5/10/2006 (Sandostatin LAR Depot) Approved Labeling[1]

Acromegaly

- Sandostatin (SAS) to reduce blood levels of growth hormone and IGF-I (somatomedin C) in acromegaly patients who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation, and bromocriptine at maximally tolerated doses.
- Sandostatin LAR Depot (SAS-LAR) for long-term maintenance therapy in acromegalic patients for whom medical treatment is appropriate and who have been shown to respond to and can tolerate SAS.

Carcinoid Tumors

- SAS for the symptomatic treatment of patients with metastatic carcinoid tumors where it suppresses or inhibits the severe diarrhea and flushing episodes associated with the disease.
- SAS-LAR for long-term treatment of the severe diarrhea and flushing episodes associated with metastatic carcinoid tumors in patients in whom initial treatment with SAS has been shown to be effective and tolerated.

Vasoactive Intestinal Peptide Tumors (VIPomas)

- SAS for the treatment of profuse water diarrhea associated with VIP-secreting tumors
- SAS-LAR for the long-term treatment of the profuse watery diarrhea associated with VIP-secreting tumors in patients in whom initial treatment with SAS has been shown to be effective and tolerated.

[1] Drugs@FDA [database on the Internet]. Silver Spring (MD): FDA Center for Drug Evaluation and Research. c2007 [cited 2007 Jan 30]. Available from: www.accessdata.fda.gov/scripts/cder/drugsatfda.

3.3 Pediatric Labeling

3.3.1 Pediatric Mentions in Octreotide Labeling[1]

This section describes Sandostatin LAR Depot (SAS-LAR) and Sandostatin (SAS) labeling (Prescribing Information) specifically related to the pediatric population. Since the labeling for SAS-LAR and SAS are different, information is presented by labeling section (such as Clinical Pharmacology) and the source (SAS-LAR or SAS) noted.

See the most recently approved labeling (available at www.accessdata.fda.gov/scripts/cder/drugsatfda) for complete prescribing information (including pharmacology, indications, contraindications, warnings, precautions, drug interactions, and adverse drug reactions).

CLINICAL PHARMACOLOGY (**Sandostatin LAR** Prescribing Information)

Pharmacokinetics, 2. Pharmacokinetics of Sandostatin LAR Depot

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.

PRECAUTIONS

Pregnancy Category B (**Sandostatin LAR and Sandostatin** Prescribing Information)

Reproduction studies have been performed in rats and rabbits at doses up to 16 times the highest human dose based on body surface area and have revealed no evidence of impaired fertility or harm to the fetus due to octreotide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers (**Sandostatin LAR and Sandostatin** Prescribing Information)

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in milk, caution should be exercised when octreotide acetate is administered to a nursing woman.

Pediatric Use (**Sandostatin LAR** Prescribing Information)

The efficacy and safety of Sandostatin LAR Depot were examined in a randomized, doubleblind, 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/m2 in Sandostatin LAR Depot–treated subjects compared to 0.0 kg/m2 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 adult indications such as acromegaly (22%) or malignant carcinoid syndrome (24%), where Sandostatin LAR Depot dosing was 10 to 30 mg once a month.

Experience with Sandostatin Injection in the pediatric population is limited. Its use has been primarily in patients with congenital hyperinsulinism (also called nesidioblastosis). The youngest patient to receive the drug was 1 month old. At doses of 1-40 mcg/kg body weight/day, the majority of side effects observed were gastrointestinal- steatorrhea, diarrhea, vomiting and abdominal distention. Poor growth has been reported in several patients treated with Sandostatin® Injection for more than 1 year; catch-up growth occurred after Sandostatin® Injection was discontinued. A 16-month-old male with enterocutaneous fistula developed sudden abdominal pain and increased nasogastric drainage and died 8 hours after receiving a single 100 mcg subcutaneous dose of Sandostatin® Injection.

Pediatric Use (**Sandostatin** Prescribing Information)

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®.

3.3.2 Safety-Related Updates to Product Labeling Since Pediatric Exclusivity Granted

Other than the addition of results from the double-blind, placebo-controlled six-month study in pediatric patients with hypothalamic obesity, no safety-related labeling updates (relevant to the pediatric population) were made during the one-year period following the date pediatric exclusivity was granted for Sandostatin LAR Depot.

3.4 Pediatric Filing History (Table 3)

Table 3. Relevant Regulatory Activity for Pediatric Use of Sandostatin LAR Depot [2]

Date	Regulatory Activity
Jan 12, 2006	Pediatric Exclusivity Granted
Jan 7, 2004	FDA issues Written Request to Novartis to conduct pediatric studies using SAS-LAR for the treatment of pediatric hypothalamic obesity.
Jan 31, 2000 – Jun 27, 2003	FDA evaluates four sponsor-submitted Proposed Pediatric Study Requests (PPSRs) for octreotide (three for pediatric hypothalamic obesity and one for obesity and primary insulin hypersecretion).

[2] Craig EM. Clinical review: octreotide acetate for injectable suspension. 2006 May 3.

4. AERS SEARCH RESULTS

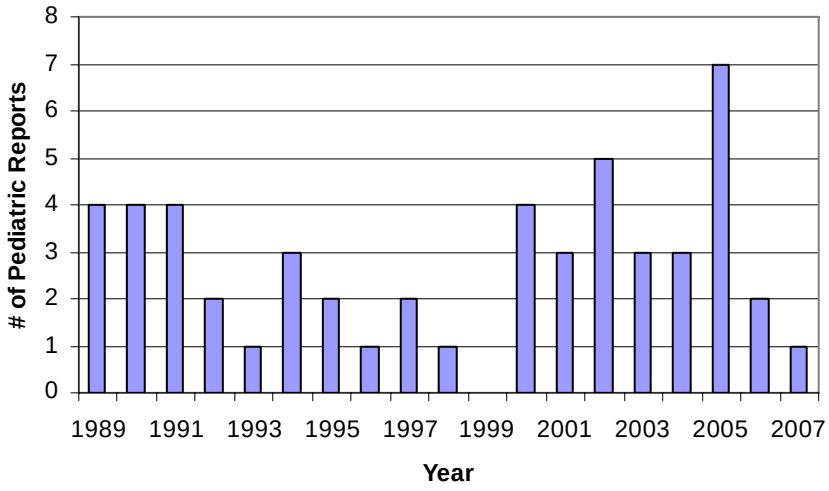
4.1 Count of Reports: AERS Search for Octreotide Reports Since Approval (Table 4)

Table 4. Crude Counts* of Octreotide (Sandostatin LAR Depot and Sandostatin) Reports in the AERS Database for All Sources Since Approval (October 21, 1988) through AERS Cutoff Date (February 12, 2007).

Age	All reports (US)	Serious† (US)	Death (US)
Adults (≥ 17 yrs)	911 (591)	654 (346)	173 (76)
Peds (0-16 yrs)	52 (33)	33 (14)	11 (4)
Age Unknown (Null)	316 (227)	172 (84)	28 (11)
Total	1279 (851)	859 (444)	212 (91)

*May include duplicates
†Serious outcomes per regulatory definition (CFR 314.80), which includes death, hospitalization, life-threatening, disability, congenital anomaly, and requiring intervention

4.2 Reporting Trend For Octreotide (Sandostatin LAR Depot and Sandostatin) Pediatric Reports (n=52) Received by FDA Since Approval (October 21, 1988 through AERS cut off date of February 12, 2007)



4.3 Count of Reports: AERS Search for Octreotide Reports During One-Year Period Following Date Pediatric Exclusivity Granted for Sandostatin LAR Depot (Table 5)

Table 5. Crude counts* of Octreotide (Sandostatin LAR Depot and Sandostatin) Reports in the AERS Database for All Sources From Date Pediatric Exclusivity Granted for SAS-LAR (January 12, 2006) through AERS Cutoff Date (February 12, 2007)

Age	All reports (US)	Serious† (US)	Death (US)
Adults (≥ 17 yrs)	85 (53)	85 (53)	17 (11)
Peds (0-16 yrs)	2 (0)	2 (0)	1 (0)
Age Unknown (Null)	40 (22)	34 (16)	6 (3)
Total	127 (75)	121 (69)	24 (14)

*May include duplicates
†Serious outcomes per regulatory definition (CFR 314.80), which includes death, hospitalization, life-threatening, disability, congenital anomaly, and requiring intervention.

5. REVIEW OF POSTMARKETING OCTREOTIDE PEDIATRIC ADVERSE EVENT REPORTS

5.1 Reports Received During the One-Year Period Following the Date Pediatric Exclusivity Granted for Sandostatin LAR Depot

FDA received one pediatric adverse event associated with Sandostatin LAR Depot (SAS-LAR) during the one-year period following the date pediatric exclusivity for SAS-LAR was granted (January 12, 2006 through February 12, 2007). This report involves a 20-day-old male (ISR 5216933) with congenital nesidioblastoma (on diazoxide) who experienced "**tachycardia, edema, fever (38-39.3 C), and vasodilation**" 12 hours after receiving 6 mg of octreotide (SAS-LAR). The report does not indicate that the infant received any doses of Sandostatin (SAS) before starting SAS-LAR. Four days later, a blood culture revealed staphylococcus epidermidis, which was successfully treated with antibiotics.

During this one-year period following the date pediatric exclusivity for SAS-LAR was granted, FDA also received one pediatric adverse event report associated with Sandostatin (SAS). This report (ISR 4981645) is a published case report involving a premature infant (delivered at 30 weeks gestation) with history of Noonan syndrome, respiratory distress (requiring surfactant replacement and ventilatory support), and congenital chylothorax (with inadequate response to chemical pleurodesis). At 106 days of age, octreotide was started and gradually titrated to 18 mcg/kg/hr. About two weeks after starting octreotide, the baby developed **abdominal distention** so the 6 AM medium chain triglyerides (MCT) was withheld. **Hypoglycemia** (< 20 mg/dL) developed 2.5 hours later, and octreotide was discontinued. Hypoglycemia (22-29 mg/dL) persisted, and glucose infusion of 6 mg/kg/min was required to maintain glucose level > 60 mg/dL. Pneumothorax occurred at 127 days of age, and the infant died "due to hypoglycemia, anuria, pneumothorax, and cardiac arrest."

5.2 Reported Characteristics, Indications and Adverse Events for Pediatric Octreotide Adverse Event Reports Received by FDA (n=52)

Since initial marketing approval of octreotide in 1988 through February 12, 2007, FDA received 52 adverse event reports associated with octreotide use in pediatric patients (including the two reports discussed above that were received during the one-year period following the date pediatric exclusivity was granted for SAS-LAR). Characteristics of these 52 reports are presented in Table 6, reported indications for use in Table 7, reports with serious outcomes attributed to the adverse event in Table 8, and a tabulation of all reported adverse events (designated as labeled or unlabeled) in Table 9.

5.2.1. Characteristics of Pediatric Octreotide Reports (Table 6)

Table 6. Characteristics of Pediatric Octreotide (Sandostatin LAR Depot and Sandostatin) Reports in the AERS Database (initial marketing approval of octreotide on October 21, 1988 through AERS cutoff date of February 12, 2007)

Characteristic	**Total Reports**
Number of Unique Reports	**52**
Origin of Reports	
United States	**33**
Foreign	**19**
Octreotide Product	
Sandostatin (SAS)	**49**
Sandostatin LAR Depot (SAS-LAR)	**1**
Unknown	**2**
Gender	
Male	**31**
Female	**18**
Unknown Gender	**3**
Age At Time of Event	Average: 5.5 years; **Median: 3 years**; Range: newborn to 16 years
< 2 years	**24**
< 1 month (n=6)	
1 month - < 1 year (n=11)	
1 year - < 2 year (n=7)	
2-5 years	**6**
6-11 years	**11**
12-16 years	**11**
Unknown Age	**0**
Daily Dose (mcg/day) for IV/SC Formulation	
< 2 years	**Median: 12 mcg/kg; Range: 0.6 - 432 mcg/kg** (n= 14; unk dose: 8)
Reports by highest administered dose:	
< 10 mcg/kg/day (n=5)	
10-19 mcg/kg/day (n=3)	
20-40 mcg/kg/day (n=2)	
>40 mcg/kg/day (n=4)	
2-5 years	**Median: 75 mcg; Range: 24 - 150 mcg** (n= 4; unk dose: 2)
6-11 years	**Median: 120; Range: 50 - 1500 mcg** (n= 10; unk dose: 1)
12-16 years	**Median: 200 mcg; Range: 40 - 1200 mcg** (n= 8; unk dose: 3)
Daily Dose (In Utero Exposure) (mother on octreotide for "hypophysis macroedema")	500 mcg daily w/ 1 dose of 10 mg monthly (n=1)
Monthly Dose for IM Formulation (mg)	6 mg (n=1)

Table 6. Characteristics of Pediatric Octreotide (Sandostatin LAR Depot and Sandostatin) Reports in the AERS Database (initial marketing approval of octreotide on October 21, 1988 through AERS cutoff date of February 12, 2007)	
Characteristic	**Total Reports**
Route of Octreotide Administration	
Injection (Infusion or Intravenous)*	**21**
Subcutaneous	**19**
Subcutaneous or Injection	**8**
Intramuscular	**1**
In Utero Exposure	**1**
Unknown	**2**
Exposure Time To Event (Or Duration of Therapy if Exposure Time Not Reported)	
	Average: 26.5 days; **Median 6 days**; Range: few minutes to 1 year
≤ 1 day	**14**
2 - 7 days	**9**
8 – 30 days	**10**
> 30 days	**7**
Unknown	**10**
Other	
In utero exposure time: ≥ 6 months	**1**
Medication Error (not applicable)	**1**
Reported Outcomes (numbers may not sum due to reports describing more than one outcome)	
Congenital Anomaly	**0**
Death	**11**
Disability	**1**
Hospitalization	**16**
Life-Threatening	**3**
Required Intervention	**5**
Other/Unknown/Not Reported	**30**

***** at least 6 received octreotide as a continuous infusion

5.2.2. Reported Indications for Use (Table 7)

There are no approved pediatric indications (including acromegaly) for either Sandostatin LAR Depot or Sandostatin. Table 7 below summarizes the reported indications for octreotide use in the 52 pediatric adverse event reports received by FDA.

Table 7. Reported Indications For Octreotide (Sandostatin LAR Depot and Sandostatin) Use (As Described in Octreotide Pediatric Adverse Event Reports). Categorized by Age and System Organ Class
Source: AERS Database (initial marketing approval of octreotide on October 21, 1988 through AERS cutoff date of February 12, 2007)

Reported Indication	**Age**		**Total Reports (n=52)**
	< 2 Years (n=24)	**2 – 16 Years** (n=28)	
Endocrine Disorders (3)			
Acromegaly	0	1	**1**
Pituitary Macroadenoma	0	2	**2**
Respiratory, Thoracic and Mediastinal Disorders (5)			
Chylothorax	4	1	**5**
Gastrointestinal Disorders (30)			
Diarrhea	2	5	**7**
Fistula (Enterocutaneous 6, Pancreatic 1)	5	2	**7**
Dumping Syndrome	0	3	**3**
GI Motility Problem, Unspecified	2	0	**2**
Hemorrhage, GI	1	1	**2**
Pancreatic Pseudocyst	0	2	**2**
Pancreatitis	0	2	**2**
Short Bowel Syndrome	0	2	**2**
Gastric Ulcer Restoration	0	1	**1**
Gastroenteropthy, Autoimmune	0	1	**1**
Pancreas, Hypersecretory	1	0	**1**
Metabolism and Nutrition Disorders (7)			
Congenital Hyperinsulinism/Nesidioblastosis	7	0	**7**
Pregnancy, Puerperium, and Perinatal Conditions (1)			
In-Utero Exposure (mother on octreotide for "hypophysis macroedema")	1	0	**1**
Vascular Disorders (2)			
Hemorrhage, Unspecified	0	1	**1**
Lympoedema	0	1	**1**
Unknown Indication (4)	1	3	**4**

5.2.3. Reports With Serious Outcomes Attributed to Adverse Event (Table 8)

As presented in Table 4 above, 33 (crude counts) of the 52 reports were designated as serious by the reporter. The remaining 19 of the 52 reports did not clearly specify the outcome. However, a hands-on review of all 52 reports identified an additional three reports with serious adverse events. Table 8 presents the 36 reports with serious outcomes attributed to the adverse event.

Table 8. Pediatric Octreotide (Sandostatin LAR or Sandostatin) Reports With Serious Outcomes
Source: AERS, initial marketing of octreotide in 1988 through February 12, 2007

ISR #	Adverse Event 1	Adverse Event 2	Adverse Event 3	Death
702976	Sepsis	Inc LFTs	Lethargy	
750664	Hypokalemia	Hyponatremia	Hypomagnesemia	
1492190	Hypoxia ("stopped breathing")			
1508983	Medication Error			
1678459	Pyrexia			
1695734	Abdominal pain	Cardiopulmonary arrest	Multi-organ failure	✓
1759121	Pyrexia			
1901274	Injection reaction	Lethargy	Weakness	
1941146	Encephalopathy, metabolic	Confusion	Weakness	
3448249	Hypoxia (“persistent need for oxygen”)	Pneumonia	Cataracts	
3489504	Bradycardia			
3502944	Necrotizing enterocolitis	Hypoglycemia	Hyperglycemia	✓
3594868	Hyponatremia			
3731667	Inc LFTs	Hypopituitarism	Hypothyroidism	
3746069	Condition, deterioration			✓
3762250	Hypoxia			
3862061	Diabetes insipidus	Cavernous sinus syndrome	Nerve palsies	
3893109	Bleeding, duodenal ulcer			✓
3962411	Hepatitis			✓
3965028	Eosinophilia	Dysrhythmia	Palpitation/HR Change	
4092714	Hypoxia	Pulmonary HTN		✓
4093023	Hypoxia	Pulmonary HTN		
4174386	Necrotizing enterocolitis	Atrial thrombus		✓
4394129	Premature baby	Respiratory insufficiency		
4499066	Pancreatitis			
4505297	Bradycardia			
4614810	AV block			✓
4648637	Thrombotic microangiopathy			
4693376	Necrotizing enterocolitis	Abdominal distention	Pyrexia, vomiting	
4761445	Dependency			
4837999	Inc LFTs	Hepatic failure		✓
4845469	Chest pain	Shortness of breath	Dizziness	
4865970	Abdominal pain	Respiratory distress	GI hemorrhagic necrosis	✓
4870923	Inc CK	Pyrexia	Inc LFTs	
4981645	Abdominal distention	Pneumothorax	Hypoglycemia	✓
5216933	Tachycardia	Edema	Pyrexia	

5.2.4. Tabulation of Reported Adverse Events (Table 9)

Table 9 below summarizes the reported adverse events in the 52 pediatric octreotide adverse event reports received by FDA between initial marketing approval of octreotide on October 22, 1988 and the AERS cut off date of February 12, 2007. The numbers may not sum because the 52 reports may describe more than one adverse event associated with octreotide use.

Table 9. Reported Adverse Events Occurring in Pediatric Patients Using Octreotide (Sandostatin LAR Depot or Sandostatin). Unlabeled adverse events are bolded. *Adverse events that are described in either the SAS-LAR or SAS labeling (but not both) are italicized.*
Source: AERS (marketing approval through 2/12/2007)

Reported Adverse Event (Categorized by System Organ Class)	**Total Reports**
Blood and Lymphatic Disorders **Eosinophilia** (1), **Neutropenia** (1) **Thrombotic microangiopathy** (1)	**3**
Cardiac Disorders **Atrial thrombus** (1) Bradycardia (2), Tachycardia (2), HR Change (1), Palpitation (1) *Cardiopulmonary arrest* [a] (1) Chest pain (1) Arrhythmia (1), **AV block**[c] (1)	**11**
Congenital, Familial and Genetic Disorders	0
Ear and Labyrinth Disorders	0
Endocrine Disorders Diabetes insipidus (1) Hypothyroidism (2)	**3**
Eye Disorders **Cataracts** (1)	**1**
Gastrointestinal Disorders Abdominal pain (3), Abdominal Distension (2), Vomiting (3) **Duodenal ulcer hemorrhage** (1) **GI hemorrhagic necrosis** (1) **Necrotizing enterocolitis** (3) Pancreatitis (1)	**14**
General Disorders & Admin Site Conditions Condition, aggravated (1) Edema (1) Injection site reaction (2), Injection site pain (3) **Multi-organ failure** (1) **Peripheral coldness**[d] (1) *Fever (Pyrexia)*[a] (5)	**14**
Hepatobiliary Disorders Hepatitis (1) **Hepatic failure** (1)	**2**
Immune System Disorders	**0**
Infections and Infestations **Sepsis** (1)	**1**
Injury, Poisoning,& Procedural Complications	0

Table 9. Reported Adverse Events Occurring in Pediatric Patients Using Octreotide (Sandostatin LAR Depot or Sandostatin). Unlabeled adverse events are bolded. *Adverse events that are described in either the SAS-LAR or SAS labeling (but not both) are italicized.*
Source: AERS (marketing approval through 2/12/2007)

Reported Adverse Event (Categorized by System Organ Class)	Total Reports
Investigations Increased CK (1) Increased liver enzymes (4)	**5**
Metabolism and Nutrition Disorders Hypoglycemia (2), Hyperglycemia (1) *Hypokalemia*[a] (1), **Hyponatremia** (3),**Hypomagnesemia** (1) **Hypopituitarism** (1)	**9**
Musculoskeletal & Connect Tissue Disorders Growth retardation (1) *Weakness*[b] (2)	**3**
Neoplasms Benign, Malignant, & Unspec	0
Nervous System Disorders Amnesia (1) **Cavernous Sinus Syndrome** (1) Dizziness (1) **Encephalopathy** (1) **Lethargy** (2), *Somnolence*[a] (1) *Paresthesia* [a] (1)	**8**
Pregnancy, Puerperium, & Perinatal Conditions **Premature Baby** (1)	**1**
Psychiatric Disorders *Confusion*[a] (1), **Hyperactivity/Irritability** (1) **Dependency**[e] (1)	**3**
Renal and Urinary Disorders	0
Reproductive System and Breast Disorders	0
Respiratory, Thoracic & Mediastinal Disorders **Hypoxia** (5) Pneumonia (1) *Pneumothorax*[a] (1) *Pulmonary hypertension*[a] (2) **Respiratory distress** (1), **Respiratory insufficiency** (1) Shortness of breath/Dyspnea (1) **Tachypnea** (1)	**13**
Skin and Subcutaneous Tissue Disorders Alopecia (2), **Hair color changes** (1) Rash (1), **Skin exfoliation,** fingertips (1)	**5**
Social Circumstances	0
Surgical and Medical Procedures	0
Vascular Disorders Hypotension[f] (1), Blood Pressure Change, NOS (1)	**2**

[a] Labeled only for Sandostatin LAR
[b] Labeled only for Sandostatin
[c] Labeled as "conduction abnormalities" in acromegalics and/or carcinoid syndrome patients
[d] Labeled for Raynaud's
[e] Discussed in labeling (no indication that octreotide has potential for dependence or abuse)
[f] Labeled as orthostatic hypotension or orthostatic BP decrease

5.3 Description of Reported Unlabeled Adverse Events

This section provides more detail on the unlabeled adverse events identified in the 52 pediatric octreotide adverse event reports (and presented in Table 9). The unlabeled adverse events are categorized by System Organ Class [SOC]), but reports may be discussed in more than one SOC since some of the reports describe more than one unlabeled adverse event. This section, within each SOC below, also provides a comparison of similar adult reports in the United States.

Eight reported events are labeled for either Sandostatin LAR Depot or Sandostatin (but not both), and are not discussed below. Sandostatin, but not Sandostatin LAR Depot is labeled for weakness. Sandostatin LAR Depot, but not Sandostatin, is labeled for seven reported events: cardiopulmonary arrest, confusion, hypokalemia, paresthesia, pneumothorax, fever, and somnolence.

5.3.1 Blood and Lymphatic Disorders

The Blood and Lymphatic Disorders System Organ Class (SOC) contains three reported unlabeled events in pediatrics: eosinophilia, neutropenia, and thrombotic microangiopathy.

5.3.1.1 Pediatric Reports

An 8-month-old male (ISR 3965028) experienced an "adverse drug reaction" that consisted of **eosinophilia**, dysrhythmia, palpitation, and heart rate change. The boy was defibrillated and treated with drug cardioconversion. The octreotide dose, exposure time, and medical history is unknown.

A 3-year-old female (ISR 589676) with secretory diarrhea secondary to ganglioneuroblastoma experienced **neutropenia** (ANC 374) a week after starting octreotide 150 mcg SC daily. WBC was normal before starting octreotide, and the child had a history of recent metronidazole and amoxicillin use.

A 12-year-old male (ISR 4648637) hospitalized with hepatic contusion and pancreatic body fracture secondary to road traffic accident experienced **thrombotic microangiopathy** "without renal insufficiency or neurological sign" one day after octreotide was initiated for post-traumatic pancreatitis (about a month after hospital admission). Before starting octreotide, the hemoglobin was 12.2 and platelets 388,000. A day after starting octreotide, the hemoglobin decreased to 8.3 and platelets to 22,000. Octreotide was discontinued and a week later the platelets had increased to 450,000.

5.3.1.2 Adult Reports

AERS contains four U.S. reports of **eosinophilia** associated with ocreotide use in adults. Two of the reports provide limited information ("patient developed eosinophilia" with dose and exposure time to event unknown). The third report involves a 19-year-old female who developed eosinophilia (5 percent increase) four months after starting octreotide for dumping syndrome. The last report involves a 65-year-old-male who experienced cholestatic hepatitis thought secondary to hydrochlorothiazide use. The man developed complications following ERCP, and octreotide was administered for about 10 hours. Later that day, he experienced

abdominal distension, hypotension, declined rapidly, and died 10 days later. The liver biopsy revealed hepatocellular and cholestatic injury with tissue eosinophilia suggestive of drug-induced injury. An association between the liver injury and hydrochlorothiazide, octreotide, or other concurrent medications is not clear.

AERS contains five U.S. reports of **neutropenia** associated with octreotide use in adults. All five reports are associated with the use of chemotherapy or chemoradiation prior to the onset of neutropenia (four of the reports were part of clinical studies assessing the efficacy of Sandostatin LAR Depot in chemotherapy-induced diarrhea).

AERS does not contain additional reports of **thrombotic microangiopathy** associated with octreotide use in adults. Thrombocytopenia and anemia are labeled events for Sandostatin LAR Depot; iron-deficiency anemia (but not thrombocytopenia) is a labeled event for Sandostatin.

5.3.2 Cardiac Disorders

The Cardiac Disorders System Organ Class contains two reported unlabeled events in pediatrics: atrial thrombus and AV block.

5.3.2.1 Pediatric Reports

A 1-month-old female (ISR 4174386) with history of respiratory distress and arterial switch procedure on day 5 started octreotide on day 23 for chylothorax. Octreotide titrated to 8 mcg/kg/hr (continuous infusion) two days prior to her death. On the day prior to her death, octreotide was stopped due to increasing abdominal distension "secondary to probable necrotizing enterocolitis and pneumatosis." The infant continued to be hypotensive and acidotic. Support was withdrawn and she died on day 31 of "respiratory and renal failure." A cardiac echo on day 29 had revealed a mobile, but attached **mass in the right atrium**." However, autopsy did not identify a mass or thrombus in the right atrium or lungs.

A 1-year-old male (ISR 4614810) with history of hypertrophic nonobstructive cardiomyopathy and possible unknown metabolic disease experienced intermittent second degree **atrioventricular block** ("Mobitz type") after three days of octreotide therapy (subsequently titrated to 60 mcg daily) that was initiated for "chylothorax and generalized edema." Interruption of octreotide therapy resulted in improvement. However, octreotide was restarted for treatment of "chylothorax, recurrent pleural effusions and ascites." The boy died at 15-months of age. The cause of death was stated as "hypertrophic cardiomyopathy and mitral stenosis based on a metabolic disorder, suspicion of lysosomal metabolic storage disease."

5.3.2.2 Adult Reports

AERS does not contain any reports of **atrial thrombus** or intracardiac thrombus associated with octreotide use in adults.

AERS contains one U.S. report of **AV block** associated with octreotide 50 mcg bolus administered for gastrointestinal bleed in a 47-yom with unknown medical history. There is also a published case report involving a 67-year-old-man who experienced hemodynamic sequelae (including bradycardia [35-45 BPM], Mobitz type II and third degree atrioventricular block) following the administration of octreotide during surgery for carcinoid tumor resection.[3] The authors outline the plausibility and suggest the severe bradycardia was caused because a "large dose of octreotide" (≥100 mcg) was administered rapidly as an intravenous bolus.

Both the Sandostatin and Sandostatin LAR labeling state cardiac conduction abnormalities occur with octreotide, but do not specifically state atrioventricular block.

5.3.3 Eye Disorders

The Eye Disorders System Organ Class contains one reported unlabeled event in pediatrics: cataracts.

5.3.3.1 Pediatric Reports

A pediatric gastroenterologist reports an 11-month-old (ISR 3448249) experienced **cataracts** (type not specified) two weeks after octreotide was initiated for an unspecified "GI motility problem." The reporter felt there was a temporal relationship between octreotide therapy and the cataracts, but notes cataracts may be a consequence of congenital abnormalities.

5.3.3.2 Adult Reports

AERS contains two U.S. reports of **cataracts** associated with octreotide use in adults. One report involves a 62-year-old female with medical history of arthritis and carcinoid syndrome who received Sandostatin LAR Depot (SAS-LAR) 10-20 mg every 28 days for about 10 months (also taking "cortisone," metoprolol, and lorazepam for unknown duration). An exam by an ophthalmologist after six months of SAS-LAR therapy revealed "no indication of cataracts." However, four months later, she was diagnosed with "cataracts, lowest degree." The other report of cataracts involves a 65-year-old male who received two doses of SAS-LAR for carcinoid syndrome. He experienced nausea, vomiting, blurry vision and light-headedness the day after administration, and refused additional doses because he developed bilateral dense cataracts (confirmed by ophthalmologist).

The Sandostatin and Sandostatin LAR Depot labelings do not mention cataracts. However, published animal studies have identified dose-related cataracts with the intravitreal administration of octreotide.[4,5]

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[3] Dilger JH, Rho EH, Que FG, Sprung J. Octreotide-induced bradycardia and heart block during surgical resection of a carcinoid tumor. Anesth Anal 2004;98:318-20.
[4] Robertson JE, Westra I, Woltering EA, Winthrop, KL, Barrie, R, ODorisio TM, Holmes D. Intravitreal injection of octreotide acetate. J Ocul Pharmacol Ther. 1997 Apr;13(2):171-7.
[5] Lian C, Peyman GA, Conway MD, Woltering EA. Retinal toxicity of intravitreaous octreotide in the rabbit. Can J Ophthalmol 1997 Jun;32(4):229-32.

5.3.4 Gastrointestinal Disorders

The Gastrointestinal Disorders System Organ Class contains three reported unlabeled events in pediatrics: duodenal ulcer hemorrhage, GI hemorrhagic necrosis and necrotizing enterocolitis.

5.3.4.1 Pediatric Reports

A 3-year-old boy (ISR 3893109) with history of nephrotic syndrome, started octreotide infusion for an unknown indication. The following day, he experienced ”**bleeding due to duodenal ulcer**” and died within 24 hours.

A literature report describes a 15-year-old boy (ISR 4865970) with history of dyskeratosis congenita, who underwent hematopoietic stem-cell transplant after low-intensity conditioning regimen.[6] On day 0, he experienced cardiorespiratory arrest six hours after the second dose of cyclosporine (part of GVHD prophylaxis regimen). He was extubated 30 hrs later with no neurological deficit. Cyclosporine changed to mycophenolate. On day + 15, the boy developed acute skin GVHD grade I (with diarrhea, bilirubin 38 mcm/L), which progressed to grade III. On day + 31, he started octreotide (at 3 mcg/kg/day, increased to 20 mcg/kg/day). On day + 38, he experienced diarrhea more than 2000 mL/m2/day (and bilirubin increased to 58). The boy then developed severe hypotension, respiratory distress and intense abdominal pain. An ultrasound revealed ascites and thickening of intestinal wall. He was diagnosed with septic shock, and subsequently died on day + 48. Autopsy revealed "diffuse **hemorrhagic necrosis of the digestive mucosa from the stomach to rectum**" and "diffuse capillaritis of the brain and gut."

A 16-day-old male (ISR 3502944) with history of hyperinsulinism (on octreotide 12.3 mcg subcutaneously [SC] every six hours for unknown duration and furosemide secondary to diazoxide-induced fluid overload) was transferred to a children’s hospital. Two days later (day 18) octreotide was discontinued, and glucagon infusion (along with dextrose and oral feedings) was started. On day 22 the glucagon was discontinued (glucose levels: 70-100). Octreotide 0.2 mcg/kg/hr started on day 23. Two days later, nursing reports “good suck but patient arching, crying and grimacing after 2 or 3 swallows.” On day 26, glucose levels decreased so dextrose and octreotide infusion rates were increased. Oral feedings reported as “increasingly difficult.” On day 29, octreotide changed to 18 mcg SC every six hours and later increased to 20 mcg (glucose levels: 60-70). Nicardipine infusion started. On day 31, oral ”intake continues to be poor with patient in obvious distress.” Octreotide increased to 25 mcg SC every six hours. The following morning (day 32), octreotide and nicardipine are discontinued (glucose levels: 317-467). The child is taken to the operating room where **necrotizing enterocolitis** “was found from gastroesophageal junction to rectum,” and the child died a few hours later.

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[6] Brazzola P, Duval M, Fournet JC, Gauvin F, Dalle JH, Champagne J, Champagne MA. Fatal diffuse capillaritis after hematopoietic stem-cell transplantation for dyskeratosis congenital despite low-intensity conditioning regimen. Bone Marrow Transplant. 2005 Dec;36(12):1103-5

A 1-month-old female (born at 38-week gestation) (ISR 4174386) with history of respiratory distress and arterial switch procedure on day 5, started octreotide on day 23 for chylothorax. On day 29, octreotide increased to 8 mcg/kg/hr. On day 30, she experienced "increasing abdominal distension secondary to probable **necrotizing enterocolitis** and pneumatosis as well as portal air" so octreotide and feedings were discontinued. The child's increasing abdominal distension "compromised respiratory, renal and cardiac functioning." Despite aggressive resuscitation, she continued to be hypotensive and acidotic. Support was withdrawn and the infant died on day 31 of "respiratory and renal failure." The autopsy revealed bilateral chylothorax, extensive necrosis and calcification of the liver, acute renal tubular necrosis, and diffuse alveolar damage. A cardiac echo on day 29 had revealed a mobile, but attached mass in the right atrium." However, the autopsy did not identify a mass or thrombus in the right atrium or lungs.

A literature report describes a newborn male with Apgar score of 9 at 1 and 5 minutes (ISR 4693376) and surgical repair of aortic coarctation on day 2.[7] Following surgery, "temporary abdominal distention was present without any other signs of necrotizing enterocolitis." On post-op day 8, the infant started enteral feedings and breast milk as parenteral nutrition was tapered. On post-op day 14, the infant was diagnosed with pleural effusion (chylothorax) which was eventually treated with octreotide 2-4 mcg/kg/hour. Within 72 hours of starting ocreotide, the infant developed abdominal distention, fever, vomiting, and bloody stools. Laboratory and radiographic testing revealed bowel wall pneumatosis, neutropenia, thrombocytopenia, and elevated C-reactive protein and lactate ("consistent with **necrotizing enterocolitis**"). Octreotide and nasogastric feeding was stopped, and antibiotics and parenteral nutrition started. The infant "responded well" and was discharged at 2 months of age "with no obvious abdominal sequelae." The authors suggest a link between octreotide effects (reduction of gastrointestinal [splanchnic] blood flow) and development of necrotizing enterocolitis, and recommend octreotide be "limited to patients with stable hemodynamic findings without recent history of compromised splanchnic perfusion."

5.3.4.2 Adult Reports

AERS does not contain U.S. reports of **gastrointestinal necrosis, necrotizing colitis, duodenal ulcer hemorrhage, hemorrhagic enterocolitis, or gastrointestinal mucosal necrosis** associated with octreotide use in adults.

5.3.5 General Disorders and Administration Site Conditions

The General Disorders and Administration Site Conditions SOC contains two reported unlabeled events in pediatrics: multi-organ failure and peripheral coldness.

5.3.5.1 Pediatric Reports

A 16-month-old male (ISR 1695734) with history of aganglionosis of the colon underwent a colectomy and developed signs of intestinal obstruction eight days later. The boy eventually

[7] Mohseni-Bod H, Macrae D, Slavik Z. Somatostatin analog (octreotide) in management of neonatal postoperative chylothorax: is it safe? Pediatr Crit Care Med 2004;5:356-357.

developed enterocutaneous fistula; the intestinal obstruction persisted. Octreotide 100 mcg was administered subcutaneously, and eight hours later the boy developed sudden abdominal pain and died suddenly. The reporter felt that the death was due to "**multisystemic organic failure** and a possible intracranial hemorrhage."

An 11-year-old boy (ISR 1547462) experienced "very **cold feet and hands**" an hour after each dose of intravenously administered octreotide.

5.3.5.2 Adult Reports

AERS contains one U.S. report of **multi-organ failure** associated with octreotide use in an adult. An 84-year-old man with multiple medical conditions, on octreotide for unknown indication and duration, was hospitalized with shortness of breath. While in the hospital, he declined and subsequently died. The "overall pattern suggested multisystem failure."

AERS does not contain any U.S. reports of **peripheral coldness** associated with octreotide use in adults. Both Sandostatin and Sandostatin LAR Depot are labeled for Raynaud's syndrome.

5.3.6 Hepatobiliary Disorders

The Hepatobiliary Disorders SOC contains one reported unlabeled adverse event in pediatrics: hepatic failure.

5.3.6.1 Pediatric Reports

A 7-month-old female (ISR 4837999) with "abnormal GI motility unable to tolerate oral feeds" (on chronic TPN) and elevated baseline "bilirubin and liver enzymes" (total bilirubin 31, BUN 19, AST 413, ALT 283, GGT 79) experienced increased bilirubin (37.9) and enzymes within a week of starting octreotide and erythromycin ethylsuccinate. Octreotide discontinued (erythyromycin continued) and the infant died five days later of **hepatic failure**.

5.3.6.2 Adult Reports

AERS contains six U.S. reports of **hepatic failure** associated with octreotide use in adults. The first report (from the NIH-sponsored Drug-Induced Liver Injury Network [DILIN]) involves a 67-year-old female with diabetes mellitus, chronic renal insufficiency, anemia, and coronary artery disease, who experienced "cholestatic liver failure" (AST 385, ALT 332, total bilirubin 49) less than a week after starting octreotide infusion for "persistent GI bleeding." She received supportive medical care, and her liver enzymes were normalizing (AST 25, ALT 45, total bilirubin 6.6) at the time of discharge from the hospital. The other five reports have underlying liver disease or provide limited information. For example, two reports involve liver failure associated with underlying carcinoid syndrome. Two other reports indicated octreotide was being used for management of esophageal varices - one patient with underlying liver cirrhosis, and the other with "alcoholism." The last report involves a 50-year-old male with a fistula who was using octreotide for "idiopathic

abdominal pain," and experienced elevated LFTs, hepatitis, and liver failure, and died an unknown time after starting octreotide.

Both Sandostatin and Sandostatin LAR Depot are labeled for cholestatic hepatitis, hepatitis, jaundice, and increased liver enzymes. According to the erythromycin labeling, erythromycin has been associated with hepatic dysfunction (including increased liver enzymes and hepatitis).

5.3.7 Infections and Infestations

The Infections and Infestations SOC contains one reported unlabeled event in pediatrics: sepsis.

5.3.7.1 Pediatric Reports

A physician reports a fullterm female newborn (ISR 702976) developed hypoglycemia and respiratory distress with enlarged heart within three hours of birth. Due to elevated insulin levels, persistent hypoglycemia, and "concern about using diazoxide," octreotide was started on day 6. On day 8, the child became lethargic, **septic**, and experienced elevated GGT and alkaline phosphatase levels (which decreased as octreotide was tapered). "In order to remove the umbilical catheter," the dose of octreotide was increased to12 mcg/kg/day. During this period the "infant fed very poorly requiring nasogastric supplements." Feeding improved as octreotide was weaned, and the reporter indicates it isn't clear if the poor feeding was related to octreotide. Sepsis was successfully treated with antibiotics.

5.3.7.2 Adult Reports

AERS contains ten U.S. reports of **sepsis** associated with octreotide use in adults. Five reports involved study patients with confounding medical history such as chemoradiation, cirrhosis, diabetes, and post-cholecystectomy. Two reports had limited information (60-year-old female on octreotide subcutaneous developed abdominal pain, necrosis and sepsis). Of the three remaining reports, one was a literature report of a 37-year-old with acromegaly and history of lacerated liver at age 7 years, who developed hepatolithiasis (that was complicated with gram-negative sepsis) after seven years of octreotide therapy. Another report involves a 65-year-old man with cholestatic hepatitis thought secondary to hydrochlorothiazide, who received octreotide 50 mcg for one day. Two days later, the man developed small bowel distension and sepsis, and died a week later. The last report involves a 53-year-old man with paraganglioma who experienced an obstructed bowel following his third monthly dose of octreotide (Sandostatin LAR Depot). Octreotide discontinued; two months later the man developed a perforated bowel, became septic and died.

5.3.8 Metabolism and Nutrition Disorders

The Metabolism and Nutrition Disorders SOC contains three reported unlabeled events in pediatrics: hyponatremia, hypomagnesemia, and hypopituitarism.

5.3.8.1 Pediatric Reports

A 2.5-year-old female (ISR 750664) with autoimmune gastroenteropathy (on TPN), type 1 diabetes mellitus, and recent history of bacterial endocarditis (treated with gentamicin and ampicillin) experienced "**low levels of** potassium, **sodium and magnesium** while taking octreotide 24 mcg daily for about three weeks. The physician reporter acknowledged TPN could also have caused the electrolyte imbalance.

A 5-year-old female (ISR 818758) experienced "**hyponatremia**" an unknown time after starting octreotide for an unknown indication. The girl was also receiving gentamicin and TPN.

A 12 year old male (ISR 3594868) with history of "hereditary pancreatitis" received octreotide 2 mcg/kg/day for "acute pancreatitis crisis" for 24 hours. The following day he experienced hyponatremia (sodium 114 mEq/L), which was treated with intravenous sodium.

A 16-year-old girl (ISR 3731667) with history of acromegaly experienced **hypopituitarism** after radiotherapy 1.5 years after starting octreotide and bromocriptine.

5.3.8.2 Adult Reports

AERS contains one adult report of **hyponatremia** and one adult report of **hypomagnesemia** associated with octreotide use. The report of hyponatremia occurred in a 76-year-old female with history of metastatic carcinoid syndrome, who had been taking octreotide (Sandostatin LAR Depot) more than three years. Hypomagnesemia occurred in a 29-year-old female with history of short-bowel syndrome (secondary to resection for adenocarcinoma of the anal verge) and high (4 liters/day) intestinal output resistant to antidiarrheal and antisecretory regimens (that included octreotide). Clonidine was successfully used to reduce fluid and electrolyte imbalances.

AERS does not contain reports of **hypopituitarism** associated with octreotide use in adults.

5.3.9 Nervous System Disorders

The Nervous System Disorders SOC contains three reported unlabeled events in pediatrics: cavernous sinus syndrome, encephalopathy, and lethargy.

5.3.9.1 Pediatric Reports

A literature report describes a 12-year-old girl (ISR 3862061) with history of pituitary macroadenoma extending bilaterally into the cavernous sinuses and suprasellar cistern (with inadequate response to cabergoline and limited subtotal resection) who started octreotide for recurring headaches.[8] The following day, the girl developed acute onset of diabetes insipidus and bilateral **cavernous sinus syndrome** (CSS) with "near complete bilateral sixth and third

[8] Boulis NM, Noordmans AJ, Barkan A, Hassing J, Chandler WF. Somatropinoma infarction during octreotide therapy leading to bilateral cavernous sinus syndrome. Pituitary 2000; 3:185-188.

nerve palsies with severe bilateral ptosis and fixed and constricted pupils." MRI revealed increase in tumor size. Octreotide discontinued but restarted to control recurring headaches. Following discharge, the girl was switched to the long-acting formulation of octreotide (Sandostatin LAR Depot), and the CSS improved with an eventual return to normal cranial nerve function.

A 16-year-old boy (ISR 1941146) with history of Gardner's syndrome (underwent "several operations for intra-abdominal tumors" and taking alfa interferon) and short bowel syndrome used octreotide to manage output from an enterocutaneous fistula. After about six months of octreotide therapy, the boy was hospitalized with **encephalopathy** ("diminished mental status with confusion"). The boy recovered, and the reporter indicated the encephalopathy could be due to interferon neurotoxicity, overproduction of lactate from the blind loop, or an infectious process.

A physician reports a fullterm female newborn (ISR 702976) developed hypoglycemia and respiratory distress with enlarged heart within three hours of birth. Due to elevated insulin levels, persistent hypoglycemia, and "concern about using diazoxide," octreotide was started on day 6. On day 8, the child became **lethargic**, septic, and experienced elevated GGT and alkaline phosphatase levels (which decreased as octreotide was tapered). "In order to remove the umbilical catheter," the dose of octreotide was increased to 12 mcg/kg/day. During this period the "infant fed very poorly requiring nasogastric supplements." Feeding improved as octreotide was weaned, and the reporter indicates it isn't clear if the poor feeding was related to octreotide. Sepsis was successfully treated with antibiotics.

A 19-day-old male (ISR 1901274) with history of congenital hyperinsulinemia (insulin level 24) experienced **lethargy**, weakness and an injection site reaction while taking octreotide. Octreotide was discontinued, and the child eventually underwent a pancreatectomy.

5.3.9.2 Adult Reports

Cavernous sinus syndrome is not a searchable term in AERS, because the term is not in the Medical Dictionary for Regulatory Activities (MedDRA). However, AERS does not contain reports of multiple nerve palsies or eyelid ptosis associated with octreotide use in adults.

AERS does not contain reports of **encephalopathy** associated with octreotide use in adults.

AERS contains three U.S. reports of **lethargy** associated with octreotide use in adults. All three reports are associated with Sandostatin LAR Depot. One involved a study patient with history of non-alcoholic steatohepatitis and multiple co-morbidities who was hospitalized with lethargy and coma, and diagnosed with hepatic encephalopathy more than a year and a half after starting octreotide. Another report was a published case report of a 39-year-old man with metastatic carcinoid tumor (on octreotide and interferon) who became lethargic after his second infusion of zoledronic acid. The last report involves a 75-year-old man with carcinoid syndrome who was hospitalized for acute confusional state, agitation, lethargy, and hallucination following his third monthly dose of octreotide.

5.3.10 Pregnancy, Puerperium, and Perinatal Conditions

The Pregnancy, Puerperium, and Perinatal Conditions SOC contains one reported unlabeled adverse event in pediatrics: premature infant.

A 43-year-old mother (ISR 4394129) taking octreotide for "hypophysis macroedema" (also taking antihypertensives) reports she delivered a **premature infant** (not further specified) who "was born having respiratory insufficiency." The child was discharged home, but no additional information was provided.

AERS contains an additional ten reports of octreotide use (for indicated maternal uses like acromegaly) during pregnancy. None reported the delivery of a premature infant. All ten women were taking the long-acting form of octreotide (Sandostatin LAR Depot). Two women experienced more than one pregnancy during octreotide use. The reports describe spontaneous miscarriages (4), normal newborn (2), induced abortions (2), dilatation and curettage for blighted ovum, (1) premature labor (31st week) with unknown outcome (1), uneventful pregnancy with unknown outcome (1), gestational diabetes with delivery of large for gestational age infant (1), and glycemic dysregulation and hydramnios noted at 26 weeks of amenorrhea (1).

Both Sandostatin and Sandostatin LAR Depot are classified as Pregnancy Category B (animal studies revealed no evidence of harm to the fetus, however, there are no adequate and well-controlled studies in pregnant women).

5.3.11 Psychiatric Disorders

The Psychiatric Disorders SOC contains three reported unlabeled adverse events in pediatrics: hyperactivity, irritability, and dependency

5.3.11.1 Pediatric Reports

A 7-8 year-old-boy (ISR 709097) experienced "**hyperactivity, irritability**, hypotension, tachycardia" following a 2-hour intravenous infusion of octreotide for the management of short bowel syndrome. No additional information available.

A literature report (ISR 4761445) describes three cases of **dependency** and analgesia associated with octreotide use in patients with growth hormone-secreting tumors.[9] One of the three cases involves a 13-year-old girl with history of pituitary macoadenoma who, following two surgeries and radiotherapy, initiated octreotide 100 mcg TID, which was titrated to 300 mcg TID. The girl presented signs of craving, self-increased her octreotide to 1800 mcg daily, and "use of octreotide became a central focus" of her life (impairing daily activities like school and socialization). The girl was admitted to the hospital and weaned off octreotide over four weeks. The authors suggest octreotide exerts a dose-related analgesic

[9] Donangelo I, Roadacki M, Peixoto MC, Vaisman M, Caldas NR, Gadelha MR. Dependency and analgesia related to treatment with subcutaneous octreotide in patients with growth hormone-secreting tumors. Endocr Pract. 2004;2:107-111.

effect, that dependency is rare but should be considered, and use of long-acting analogs (like Sandostatin LAR Depot) may avoid octreotide tolerance and dependence.

5.3.11.2 Adult Reports

AERS does not contain U.S. reports of **irritability** or **hyperactivity** associated with octreotide use in adults.

Although AERS does not contain additional reports of **dependency** associated with octreotide use in adults, there are published case reports (in addition to the one described above).[10,11] Both the Sandostatin and Sandostatin LAR labeling state: *There is no indication that octreotide has potential for drug abuse or dependence. Octreotide levels in the central nervous system are negligible, even after doses up to 30,000 mcg.*

5.3.12 Respiratory, Thoracic and Mediastinal Disorders

The Respiratory, Thoracic and Mediastinal Disorders SOC contains four reported unlabeled adverse events in pediatrics: hypoxia, respiratory distress, respiratory insufficiency, and tachypnea.

5.3.12.1 Pediatric Reports

A 2-year-old male (ISR 1492190) with history of "HIV-associated diarrhea, AIDS, CHF, hypertension, thrombocytopenia, anemia and numerous other medical problems" "**stopped breathing**" after receiving octreotide 50 mcg IV over one minute (followed by rapid normal saline flush) through his port-a-cath. Caregiver stimulated breathing and administered oxygen; the child resumed breathing after 30-40 seconds. Prior to this event, registered nurses had administered octreotide (either subcutaneously or intravenously) twice daily for about 2 months.

An 11-month-old (ISR 3448249) with history of "GI motility problem" (on TPN), cataracts, and other unknown medical history, on octreotide for about two months, experienced pneumonia and "**required oxygen ever since**". The pediatric gastroenterologist questioned "if octreotide may have contributed to the child's continued need for oxygen."

A 3-month-old male (ISR 3762250) with history of enterocutaneous fistula, prematurity (born at 28 weeks gestation), short gut syndrome, and elevated LFTs (ALT 118, AST 212, alk phos 855, total bilirubin 10.5, direct bilirubin 7.2) "**desaturated** from mid-90's to Sp02 65" after receiving octreotide 1.8 mcg (administered as 9 mcg/10 mL saline infusion over 30 minutes). Infusion halted. The boy was rechallenged with a lower concentration of 7

[10] May A, Lederbogen S, Diener HC. Octreotide dependency and headache: a case report. Cephalalgia 1994 Aug;14(4):303-4.
[11] Popovic V, Paunovic VR, Micic D, Nesovic M, Kendereski A, Djordjevic P, Manojlovic D. The analgesic effect and development of dependency to somatostatin analogue (octreotide) in headache associated with acromegaly.

mcg/10 mL infusion over 30 minutes, and again "desaturated to Sp02 56." Infusion stopped and oxygen administered.

A literature report describes two cases of octreotide-induced hypoxemia and pulmonary hypertension in premature neonates.[12] The first case (ISR 4093023) involves a premature neonate (24-week gestation) with history of type I respiratory distress and bronchopulmonary dysplasia (but tolerated room air with pulse oximeter saturation of 90-100 percent) who underwent ileal resection at two months of age for necrotizing enterocolitis. Ileostomy closed at 6 months of age. On post-op day 4, bilious drainage occurred. Conservative management did not achieve closure of enterocutaneous fistula so octreotide started. During octreotide therapy, "**multiple episodes of oxygen desaturation** were noted with levels down to 60 percent within 30 minutes after octreotide administration." After seven days of octreotide therapy, the child required oxygen with improvement of oxygen saturation greater than 90 percent. Followup found "severe pulmonary hypertension with elevated right ventricular pressure of 70 mm Hg." The child was discharged home on post-op day 90 with digoxin, furosemide and oxygen supplementation. The second case (ISR 4092714) involves a 29-week-neonate with history of type I respiratory distress requiring ventilatory support for four days. He developed necrotizing enterocolitis at 3 weeks of age and underwent resection of jejunum. On post-op day 3 surgical wound dehiscence and enterocutaneous fistula were noted. Octreotide was started, and drainage ceased. However, the fistula reopened and octreotide restarted. "**Episodes of oxygen desaturation** down to 80 percent were noted," and responded to oxygen supplementation. Testing revealed "mild pulmonary hypertension." Octreotide stopped; the child improved and tolerated room air one week after octreotide was stopped. However, the child died at 6 months of age from "liver and renal failure related to his intraabdominal problem and short bowel syndrome." The authors suggest premature infants may not express the biphasic response to octreotide (initial vasoconstriction of pulmonary arterial vasculature with subsequent return to baseline) that is typically seen in adults or full-term infants. The authors recommend reducing the dose of octreotide in premature neonates, and caution when using octreotide in high-risk patients with increased pulmonary vascular resistance.

A literature report describes a 15-year-old boy (ISR 4865970) with dyskeratosis congenita who underwent hematopoietic stem-cell transplant after low-intensity conditioning regimen.[6] On day 0, he experienced cardiorespiratory arrest six hours after the second dose of cyclosporine (which was administered as part of GVHD prophylaxis). The boy was extubated with no neurological deficit. Cyclosporine changed to mycophenolate. On day + 15, the boy developed acute skin GVHD. On day + 31, octreotide was started for diarrhea. On day + 38, the boy developed severe hypotension, **respiratory distress** and intense abdominal pain. Ultrasound revealed ascites and thickening of intestinal wall. Diagnosed with septic shock, and subsequently died on day + 48. Autopsy revealed "diffuse hemorrhagic necrosis of the digestive mucosa from the stomach to rectum" and "diffuse capillaritis of the brain and gut."

[12] Arevalo RP, Bullabh P, Krauss AN, Auld PAM, Spigland N. Octreotide-induced hypoxemia and pulmonary hypertension in premature neonates. J Pediatr Surg. 2003;38 (2):251-253.

A 43-year-old mother (ISR 4394129) taking octreotide for "hypophysis macroedema" (also taking antihypertensives) reports she delivered a premature infant (not further specified) who "was born having **respiratory insufficiency**." The child was discharged home, but no additional information was provided.

A 13-year-old male (ISR 3056488) "had an adverse reaction of blood pressure change, rash, flushing, and **tachypnea**" an unknown time after receiving an unknown dose of octreotide for "gastric ulcer restoration." The boy was also receiving dopamine, fentanyl and midazolam.

5.3.12.2 Adult Reports

AERS contains six U.S. reports of **hypoxia** associated with octreotide use in adults. Three reports involve Sandostatin LAR Depot, of which two were study patients. The first study patient was a 62-year-old female with history of neuroendocrine carcinoma, atrial fibrillation and heart failure who developed hypoxia three months after starting octreotide and the study medication (RAD001). She was diagnosed with pneumonitis, paroxysmal atrial fibrillation and dyspnea. It is not clear if the events are associated with octreotide or RAD001. The second study patient was a 56-year-old man who experienced gallstones and cholecystitis eight months after starting octreotide. Octreotide was temporarily discontinued. The following year the man experienced a "gallbladder attack" and subsequently developed sepsis secondary to cholelithiasis and biliary pancreatitis. Following a cholecystectomy, he presented with hypoxemia and developed "pneumonia leading to adult respiratory distress syndrome and died shortly after. The other report involving Sandostatin LAR Depot describes a man (age unknown) who developed shortness of breath, hypoxia, dizziness, and exacerbation of existing diarrhea five days after starting octreotide. The other three reports of hypoxia involve Sandostatin, of which one is an 84-year-old man with underlying respiratory disease (COPD and "chronic respiratory failure"), coronary artery disease and gastrointestinal bleeding who experienced "worsening shortness of breath" and was found "hypoxic with no clear infiltrates" an unknown time after starting octreotide. Another one involves a 74-year-old man with history of adenocarcinoma of the transverse colon, who received octreotide while hospitalized with acute chemotherapy-associated diarrhea. Two days later he developed ventricular tachycardia (and septic shock and hypoxia), and octreotide was discontinued. The last report involves a 72-year-old man with acromegaly, who developed shortness of breath (90-91 % on 4 L of oxygen), fever, chills, and cough about four months after starting octreotide. Octreotide discontinued and "patient much improved after only one day."

AERS contains one report of **respiratory failure** and one report of **respiratory distres**s with "worsening ventilatory failure" associated with octreotide use in adults. The first report involves the 84-year-old man described in the above paragraph (under hypoxia) who had a history of "chronic respiratory failure." The other report is a published case report involving an 18-year-old boy with history of malignant thyoma who experienced worsening dyspnea and orthopnea three weeks after starting octreotide. The authors indicate the man developed a "profound autoimmune polymyositis and lupus-like syndrome that flared following treatment with octreotide"

AERS contains two reports of **tachypnea** associated with octreotide use in adults. The first involves a 36-year-old male study patient with alcoholic liver cirrhosis who developed "polypnea" a month after octreotide injection (SAS) was discontinued. The other case involves a 46-year-old female with acromegaly who experienced "acute onset of difficulty breathing" ("tachycardia with tachypnea"), and "covered in hives," an unknown time after receiving 50 mcg of octreotide subcutaneously. Final diagnosis was acute allergic reaction and acute anxiety reaction. Octreotide discontinued.

5.3.13 Skin and Subcutaneous Tissue Disorders

The Skin and Subcutaneous Tissue Disorders contains two reported unlabeled adverse events in pediatrics: hair color changes and skin exfoliation of the fingertips.

5.3.13.1 Pediatric Reports

A 7-year-old male (ISR 751063) with history of "severe recurring diarrhea," short bowel syndrome (on hyperalimentation) and recent chemotherapy regimen for an unknown indication experienced **hair color change** ("brown hair turned white and fell out"), and **skin exfoliation** ("skin on his fingertips also started to peel") within three weeks of starting octreotide 75 mcg BID.

5.3.13.2 Adult Reports

AERS does not contain additional reports of **hair color change** associated with octreotide use in adults, but does contain three U.S. reports of **skin exfoliation** associated with octreotide use in adults. The first report involves a female who experienced fluid-filled vesicles (that ruptured leading to "skin sloughing") following two-three hour infiltration of octreotide (being administered intravenously at 50 mcg/hour). The other two reports involve Sandostatin LAR Depot and are associated with a clinical study determining the efficacy of Sandostatin LAR Depot in reducing the severity of chemoradiation-induced diarrhea in patients with anal or rectal cancer (RTOG-0315). Both patients were receiving chemoradiation and experienced desquamation in the perineal area.

5.4 Deaths (Table 10)

FDA received 11 reports (3 from the United States) of death associated with octreotide use in pediatrics. Seven (64 percent) of the eleven deaths were reported in children less than two years of age. A brief summary of the 11 pediatric octreotide deaths received by FDA are provided below in Table 10 (categorized by System Organ Class). All of the 11 reports of death, except two (ISR 3962411 and ISR 3746069) are described in previous Sections (5.1 Reports Received During the One-Year Period Following the Date Pediatric Exclusivity Granted for Sandostatin LAR Depot (SAS-LAR) or 5.3 Description of Reported Unlabeled Adverse Events).

Table 10. Reported Deaths Associated With Octreotide (Sandostatin LAR Depot [SAS-LAR] or Sandostatin [SAS]) Use In Pediatric Patients. Organized by System Organ Class (SOC)
Source: AERS (marketing approval through 2/12/2007)

System Organ Class/Description of Event	Number of Deaths
Cardiac Disorders	**2**
• ISR 4614810, received 2005 1-year-old with hypertrophic nonobstructive cardiomyopathy received octreotide (titrated to 60 mcg daily) for "chylothorax and generalized edema." Three days later, the boy developed an intermittent second-degree AV block. The child died "due to history of underlying disease" about two weeks after stopping octreotide. The cause of death was “hypertrophic cardiomyopathy and mitral stenosis based on a metabolic disorder” (see Section 5.3.2.1). • ISR 4981645, received 2006 4-month-old with Noonan syndrome, respiratory distress, and congenital chylothorax. About two weeks after starting octreotide (titrated up to 18 mcg/kg/hr), the baby developed abdominal distention and persistent hypoglycemia. The infant died “due to hypoglycemia, anuria, pneumothorax, and cardiac arrest” (see Section 5.1)	
Gastrointestinal Disorders	**3**
• ISR 3893109, received 2002 3-year-old boy with nephrotic syndrome (on prednisone) started octreotide for unknown indication. The following day he experienced “multiple bleeding due to duodenal ulcer” and died within 24 hours (see 5.3.4.1). • ISR 4865970, received 2005 15-year-old with dyskeratosis congenita underwent hematopoietic stem-cell transplant. On day 0, he experienced cardiorespiratory arrest, but was extubated with no neurological deficit. On day + 31, he started octreotide (titrated to 20 mcg/kg/day). On day + 38, the boy experienced significant diarrhea, and developed severe hypotension, respiratory distress and intense abdominal pain. An ultrasound revealed ascites and thickening of intestinal wall. He subsequently died on day + 48. Autopsy revealed " diffuse hemorrhagic necrosis of the digestive mucosa from the stomach to rectum" and "diffuse capillaritis of the brain and gut" (see Section 5.3.4.1) • ISR 3502944, received 16-day-old with hyperinsulinism started octreotide (titrated to 25 mcg every six hours). On day 32, octreotide discontinued (glucose 317-467). The child was taken to the operating room where necrotizing enterocolitis “was found from gastroesophageal junction to rectum.” The child died a few hours later (see Section 5.3.4.1).	
General Disorders & Administration Site Conditions	**2**
• ISR 3746069, received 2001 6-year-old boy with leukemia experienced “deterioration in his condition” after	

Table 10. Reported Deaths Associated With Octreotide (Sandostatin LAR Depot [SAS-LAR] or Sandostatin [SAS]) Use In Pediatric Patients. Organized by System Organ Class (SOC) Source: AERS (marketing approval through 2/12/2007)	
System Organ Class/Description of Event	**Number of Deaths**
starting cyclosporine and octreotide for an unknown indication. The boy died about a year after starting cyclosporine and octreotide (cause of death not reported). • ISR 1695734, received 1996 16-month-old with enterocutaneous fistula died 8 hours after a single injection of 100 mcg octreotide. The reporter indicated the cause of death was multi-organ failure and possible intracranial hemorrhage (see Section 5.3.5.1)	
Hepatobiliary Disorders	**3**
• ISR 4837999, received 2005 7-month-old with "abnormal GI motility" (on chronic TPN) and elevated bilirubin and liver enzymes started octreotide 6 mcg every 12 hours and erythromycin ethylsuccinate. Octreotide discontinued after one week. The child died 5 days later of hepatic failure. (see Section 5.3.6.1) • ISR 3962411, received 2002 9-year-old girl with history of liver transplant x 2 on octreotide 1.5 mg daily for unspecified hemorrhage presented with "hepatitis that worsened her condition." The girl died within six weeks (cause of death not reported) • ISR 4092714, received 2003. 3-week-old boy with respiratory distress and necrotizing enterocolitis started octreotide (titrated to 3 mcg/.kg/hr) for enterocutaneous fistula following resection of jejunum. The infant died at 6 months "from liver and renal failure related to his intraabdominal problem and short bowel syndrome." (see Section 5.3.12.1)	
Respiratory, Thoracic & Mediastinal Disorders	**1**
• ISR 4174386, received 2003 1-month-old with respiratory distress and history of arterial switch procedure started octreotide (titrated to 8 mcg/kg/hr) for chylothorax. On the day prior to her death, octreotide was stopped due to increasing abdominal distension "secondary to probable necrotizing enterocolitis and pneumatosis." She later died of "respiratory and renal failure" (see Section 5.3.2.1).	

5.5 Published Pediatric Case Reports

A MEDLINE search using the terms, 'octreotide' or 'sandostatin' and limited to English, All Child (0-18 years), Case Reports, and subheading 'Adverse Effects' identified an additional adverse event report of cholestatic jaundice and cholelithiasis (both labeled events for Sandostatin and Sandostatin LAR Depot). A female premature infant (33 weeks gestational age) with hyperinsulinemia started glucose, glucagon and diazoxide (along with oral feedings).[13] Hypoglycemia continued so diazoxide was switched to octreotide (6-40 mcg/kg per day). "Liver enzymes and abdomen ultrasound were normal" the first week of life. However, after five weeks of treatment, the infant developed cholestatic jaundice and cholelithiasis (total bilirubin 3.1, ALT 152, AST 226). The octreotide dosage was decreased, diazoxide restarted, and ursodeoxycholic acid initiated. The gallstones resolved, and cholestasis parameters normalized.

[13] Radetti G, Gentili L, Paganini C, Messner H. Cholelithiasis in a newborn following treatment with the somatostatin analogue octreotide. Eur J Pediatr. 2000 Jul;159(7):550.

6. LIMITATIONS OF AERS

There may be more adverse event reports associated with octreotide use in the pediatric population. The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the United States reflects underreporting and duplicate reporting. For any given report, there is limited certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

7. SUMMARY

This review of pediatric octreotide reports in the AERS database identified off-label use, serious adverse events, and differences between the Sandostatin and Sandostatin LAR labelings.

7.1. Off-Label Use of Octreotide in Pediatric Population

Despite the lack of controlled trial data, off-label use of octreotide in the pediatric population is promoted in published literature. For example, a 2006 article for Neonatal Network includes a table, entitled, "Off-Labeled Indications and Dosage Regimens for Octreotide."[14] The table lists dosages for the following off-label indications: post-operative chylothorax, refractory hypoglycemia, GI fistula, variceal bleeding, diarrheal states, pancreatic fistula and irritable bowel syndrome. The authors state the table was "adapted from: Novartis Pharmaceuticals. 2003. Sandostatin. Octreotide acetate (product information)." In another example, an invited review described more than 10 off-label uses of octreotide in the pediatric population.[15]

Furthermore, the Pediatric Use sections of the Sandostatin LAR Depot and Sandostatin labelings describe off-label use (and associated doses) and some may misinterpret octreotide as being approved for certain uses in children.

This review of adverse event reports found octreotide was used in the pediatric population for an assortment of off-label indications, for which there are differences by age (see Table 7). Children less than 2 years of age used octreotide mainly for hyperinsulinism, fistulas, and chylothorax, followed by diarrhea or other gastrointestinal motility problem. In contrast, children older than 2 years of age used octreotide primarily for gastrointestinal disorders. Drug use data confirmed octreotide is used in the pediatric population, and associated with a wide range of Principal Diagnosis ICD9 codes in the hospital setting,[16]

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[14] Stajich GV, Ashworth L. Pointers in practical pharmacology: octreotide. Neonatal Network. 2006 Sep/Oct;25(5): 365-369.
[15] Heikenen JB, Pohl JF, Welin SL, Bucuvalas JC. Octreotide in pediatric patients. J Pediatr Gastroenterol Nutr. 2002 Nov;35(5): 600-609
[16] Pamer CA. Octreotide: drug use data for octreotide (Record # 2007-050). 2007 Mar 2.

This review of adverse event reports also identified a wide range of octreotide doses used in the pediatric population (particularly in children less than 2 years of age). Although there are no approved pediatric indications for octreotide, the Pediatric Use sections of the SAS and SAS-LAR labelings describe doses of 1 or 3 to 40 mcg/kg/day for the management of congenital hyperinsulinism. For the seven octreotide adverse event reports that listed hyperinsulinism or nesidioblastosis as the indication for use, no doses greater than 40 mcg/kg/day were reported. However, doses exceeding 40 mcg/kg/day in children less than 2 years of age were associated with the management of chylothorax (n=3) and enterocutaneous fistula (n=1). A review article on using octreotide for chylothorax in infants and children (based on published case reports and experience with three patients) promotes the "earlier use of high doses" (intravenous octreotide infusion doses of 80-100 mcg/kg/day) for as long as three weeks.[17]

The adverse event reports revealed octreotide (SAS) is administered as a continuous infusion to pediatric patients (which is also promoted in published literature[18]). Continuous infusion of octreotide has not been studied and is not a labeled method of administration in any population for any indication. The Dosage And Administration section of the Sandostatin labeling recommends infusing a diluted solution of Sandostatin over 15-30 minutes or administering by IV push over 3 minutes.

Lastly, the one adverse event report that involved SAS-LAR (20-day-old male with nesidioblastoma), the patient did not receive any doses of SAS prior to administration of SAS-LAR. The SAS-LAR labeling recommends (for approved indications) that patients not currently receiving octreotide should begin therapy with SAS before switching to SAS-LAR.

7.2. Adverse Events Associated with Octreotide Use in Pediatrics

Regardless that the pediatric octreotide adverse event reports received by FDA are associated with off-label use, the reported events are serious (including 11 deaths) and not limited to a particular System Organ Class. Nearly half of the pediatric octreotide reports received by FDA involve children less than two years of age.

Many of the reported adverse events are described in the SAS or SAS-LAR labelings. However, comparing pediatric adverse events with the SAS or SAS-LAR labelings has limited usefulness because the population studied for approved indications (e.g., acromegaly, carcinoid tumors, and VIPomas) markedly differs from the off-label use in the pediatric population. For example, FDA received pediatric reports of bradycardia and conduction abnormalities associated with octreotide use that required life-saving measures. Bradycardia and conduction abnormalities are labeled events for both SAS and SAS-LAR. However, the labelings indicate the relationship of cardiac events to octreotide is not established because the studied population (such as acromegalics) have underlying cardiac disease, or are at increased risk of cardiac disease because of the treatment they receive.

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[17] Helin RD, Angeles ST, Bhat R. Octreotide therapy for chylothorax in infants and children: a brief review. Pediatr Crit Care Med. 2006;7:576-579.

[18] Lam JC, Aters S, Tobias JD. Initial experience with octreotide in the pediatric population. Am J Ther. 2001:8(6):409-415.

For reported unlabeled events (adverse events not described in either the SAS or SAS-LAR labelings) such as hypoxia or necrotizing enterocolitis, this review did not identify similar adult cases to confirm an association between octreotide and the adverse event reported in pediatrics. However, a more comprehensive review of the adult octreotide adverse event reports received by FDA may provide additional insight. Some of the reported pediatric adverse events (such as necrotizing enterocolitis) do not typically occur in adults and similar syndromes or symptoms may be coded in AERS using other terms that were not searched. Likewise, it would be useful to evaluate all reported adult adverse events within a System Organ Class (SOC) such as Respiratory Disorders or Hepatobiliary Disorders before making a conclusion about an association between respiratory events like hypoxia and octreotide or hepatic failure and octreotide.

It is possible octreotide was directly involved in the reported adverse events such as hypoxia, cardiac dysfunction, hepatic failure, and necrotizing enterocolitis in the pediatric population. Octreotide, a somatostatin analog, is pleiotropic with inhibitory effects on growth hormone, glucagon, insulin, splanchnic blood flow, and on the release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.[1] Octreotide decreases systemic oxygen uptake in patients with cirrhosis,[19] and may cause increased pulmonary vascular pressure in premature infants.[12] Almost all the pediatric octreotide adverse event reports received by FDA are from health care professionals (including pediatric gastroenterologists and pediatric endocrinologists). There is a potential temporal relationship since 27 percent reported the adverse event occurred within 24 hours of starting octreotide. There are also reports of rechallenge – pediatric patients who reexperienced hypoxia (oxygen desaturation) with subsequent doses of octreotide. However, it is not clear how high doses, duration of therapy, or underlying conditions in the pediatric population (such as prematurity) might impact the pharmacokinetic and pharmacodynamics of octreotide. One published article questioning the safety of octreotide in neonates, recommends octreotide should be "limited to patients with stable hemodynamic findings without recent history of compromised splanchnic perfusion."[7]

The placebo-controlled study of children with hypothalamic obesity, submitted by the sponsor in response to FDA's Written Request, did not demonstrate efficacy of SAS-LAR, but revealed the incidence of new cholelithiasis is higher (SAS-LAR 33%, control 0%) in the pediatric hypothalamic obesity population compared to that seen in the adult population treated with octreotide."[2] A literature search found one report of cholestatic jaundice and cholelithiasis associated with octreotide use in a 1-month-old.[13] Cholestatic jaundice can progress to liver failure, and there are U.S. reports of hepatic failure associated with octreotide use in adults (see Section 5.3.6.2).

FDA received eleven reports of death associated with octreotide use in pediatrics. Sixty-four percent of the deaths occurred in children less than two years of age, but this review could not discern trends between pediatric octreotide use and reports of death.

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[19] Lin HC, Hou MC, Lee WC, Huang YT, Lee FY, Change FY, Tsai YT, Lee SD. Effects of octreotide on central hemodynamics and systemic oxygen use in patients with viral cirrhosis. Am J Gastroenterol 1999:94 (4):1012-1017.

Lastly, the safety of long-term octreotide use is not known, particularly during periods of growth. FDA received one report of growth retardation in a 5-month-old who received octreotide for about four months.

7.3 Differences in Sandostatin LAR and Sandostatin labelings

Sandostatin LAR Depot (SAS-LAR), which includes a comparator study with Sandostatin (SAS), lists more adverse events than the SAS labeling. The importance of the labeling differences for the pediatric population is not clear, since there are no pediatric indications and octreotide labeled adverse events are identified in specific populations such as acromegalics who may have underlying diseases or be at increased risk of diseases. However, both SAS and SAS-LAR contain Pediatric Use sections which describe the use of octreotide for congenital hyperinsulinism, and a death that occurred in a 16-month-old male who died 8 hours after receiving a single dose of Sandostatin for management of an enterocutaneous fistula. The Sandostatin LAR labeling further describes the lack of efficacy in pediatric patients with hypothalamic obesity (and the increased risk of cholelithiasis).

8. RECOMMENDATIONS

Based on the findings of this review of pediatric octreotide adverse event reports in AERS, DDRE recommends the following:

1) Communicate to health care professionals that FDA has received serious adverse events (including deaths) associated with octreotide use in pediatrics. This could be done in accordance with the FDA's guidance on communicating drug safety to the public[20] and/or brief report in a pediatric journal.

2) Revise the Pediatric Use sections in both the Sandostatin LAR Depot and Sandostatin labeling to:

    a. Clearly note there are no approved pediatric indications for octreotide.
    b. Provide consistent wording to both package inserts.
    c. Provide post-marketing updated adverse event information.

3) Engage the sponsor to:

    a. Initiate an educational campaign targeted toward specialty areas such as neonatology and pediatrics, instructing the prescribers regarding reported adverse events associated with octreotide use in the pediatric population.
    b. 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

[20] FDA Center for Drug Evaluation and Research. Guidance: communicating drug safety – FDA's communication to the public. 2007 Mar. Available at: www.fda.gov/CDER/guidance/7477fnl.pdf

c. Investigate pediatric uses of octreotide (identified above as areas of needed clinical research) in controlled settings. Clinicians or investigators willing to investigate octreotide use in the pediatric population could contact the sponsor. The sponsor already has a website for clinical trial information on their products and provides a contact number for more information on their clinical trials with Sandostatin LAR Depot. [21,22]

In a separate document, DDRE will review adult octreotide adverse event reports in AERS and make recommendations about revising both the Sandostatin LAR Depot and Sandostatin labelings.

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[21] Novartis. Clinical Trial Information For Patients and Caregivers [cited 2007 Mar 19]. Available from: www.novartisclinicaltrials.com.
[22] Novartis. Resources: Clinical trials. c2007 [cited 2007 Mar 19]. Available from: http://www.us.sandostatin.com/hcp/resources/clinical-trials.jsp.

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/s/

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