One Year Post-Exclusivity Adverse Event Review: Octreotide

Pediatric Advisory Committee Meeting
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Octreotide: Objectives

- Background information
- Drug use
- Exclusivity studies
- Serious adverse events by System Organ Class (SOC)
  - Focus on gastrointestinal, respiratory and cardiac systems
- Reported deaths by SOC
- Concerns pertaining to off-label use particularly in infants
- Questions for the Committee

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Background Drug Information: Octreotide

- **Drug:** Sandostatin® injection and LAR (octreotide)
- **Therapeutic Category:** somatostatin analogue
- **Sponsor:** Novartis
- **Original Market Approval:** Sandostatin® injection (10/21/88), Sandostatin LAR® (11/25/98)
- **Pediatric Exclusivity Granted:** January 12, 2006

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Background Drug Information: Octreotide

- Adult Indications:
  - Treatment of **acromegaly** in patients who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation and bromocriptine mesylate
  - Symptomatic treatment of patients with metastatic **carcinoid tumors** to suppress or inhibit severe diarrhea and flushing episodes
  - Treatment of profuse watery diarrhea associated with **Vasoactive Intestinal Peptide-secreting tumors**
- Pediatric Indications: none

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Drug Use Trends: Octreotide

- Use information difficult to obtain since the data resources available to the agency do not capture the use of Sandostatin LAR depot in the outpatient clinic setting, which represents approximately 54% of its use.[1]
- Premier™ database revealed pediatric use in 0.9% (156 discharges) of discharges in which octreotide was billed between July 2005 and June 2006.[2]
  - Sandostatin LAR® Depot was associated with a total of 7 pediatric discharges for the same 12 month period.[2]

[1]IMS Health, IMS National Sales Perspective™
[2]Premier Rx Market Advisor, July 2005-June 2006, Data extracted Feb 2007

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Pediatric Exclusivity Study: Sandostatin LAR® Depot

- Randomized, double-blind, placebo-controlled, fixed-dose (40 mg once a month) six-month study in 60 patients aged 6-17 years with hypothalamic obesity resulting from cranial insult.

- A six-month open label extension study

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Pediatric Exclusivity Study Efficacy Results

- Primary efficacy endpoint: mean change in Body Mass Index (BMI) from baseline
  - Sandostatin LAR; 0.1 kg/m^2 versus placebo 0.0kg/m^2 (p=0.74, not significant)
- Efficacy not demonstrated

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Pediatric Exclusivity Study Safety Results

Most frequent adverse events during Sandostatin LAR ® (SAS-LAR) treatment

Adverse event (n=30)	SAS-LAR (n=30)	Placebo
diarrhea	37% (n=11)	7% (n=2)
cholelithiasis	33% (n=10)	0% (n=0)
abdominal pain	13% (n=4)	3% (n=1)

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Pediatric Exclusivity Study Safety Results

- The incidence of new cholelithiasis (33%) in this pediatric population using 40 mg dose once a month was higher than that seen in adult indications such as acromegaly (22%) or malignant carcinoid syndrome (24%) where dosing was 10 to 30 mg once a month.
- Open-label extension study terminated due to lack of efficacy and high risk of gallstone formation.

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Labeling Changes Resulting from Exclusivity Study

- Clinical Pharmacology – data from PK study included in labeling
- Precautions – Pediatric Use
  - Data from Sandostatin LAR ® hypothalamic obesity trial:
    - No efficacy demonstrated
    - Higher incidence of new cholelithiasis

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Adverse Event Reports During the Post Exclusivity Period

Raw Counts*	All Reports (US)	Serious (US)	Death (US)
All Ages	127 (75)	121 (69)	24 (14)
Adults (≥ 17)	85 (53)	85 (53)	17 (11)
Pediatrics (0-16)	2 (0)	2 (0)	1 (0)

*May include duplicates and unknown ages
Source: Adverse Event Reporting System, FDA

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Adverse Event Reports Since Market Approval

10/21/1988 – 2/12/2007

Raw Counts*	All Reports (US)	Serious (US)	Death (US)
All Ages	1279 (851)	859 (444)	212 (91)
Adults (≥ 17)	911 (591)	654 (346)	173 (76)
Pediatrics (0-16)	52 (33)	33 (14)	11 (4)

*May include duplicates and unknown ages
Source: Adverse Event Reporting System, FDA

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Reported Uses of Octreotide in Pediatric Patients

- Uses (52)
  - Fistula – 7(enterocutaneous 6, Pancreatic 1)
  - Hyperinsulinemia/ Neisidioblastosis – 7
  - Diarrhea – 7
  - Chylothorax – 5
  - Unknown indication – 4
  - Dumping Syndrome – 3
  - Pituitary Macroadenoma – 2
  - GI Motility Problem, Unspecified – 2
  - Hemorrhage, GI – 2

Source: Adverse Event Reporting System, FDA

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Reported Uses of Octreotide in Pediatric Patients

Indications continued

- Pancreatitis – 2
- Short Bowel Syndrome - 2
- Pancreatic Pseudocyst - 2
- Gastric Ulcer Restoration – 1
- Gastroenteropathy, Autoimmune – 1
- Pancreas, hypersecretory – 1
- In-Utero Exposure – 1
- Hemorrhage, Unspecified – 1
- Lympoedema – 1
- Acromegaly – 1

Source: Adverse Event Reporting System, FDA

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Serious Adverse Events (n=36)

- Although 33 of the 52 adverse event reports were coded as serious adverse events, a hands-on review demonstrated that there are 36 reports in pediatric patients with serious adverse events.

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Serious Adverse Events (continued)

Gastrointestinal Disorders (n=2)

Two cases possibly related

- newborn male on octreotide (titrated to 4 mcg/kg/hr) for post surgical chylothorax. Day 3 developed clinical signs of necrotizing enterocolitis (NEC). Octreotide stopped. The infant did well. Discharged at 2 months.
- 11 year old male with germinoma on octreotide 100 mcg IV daily, ifosfamide and cisplatin for germinoma and abdominal pain. 2 days later, developed pancreatitis. Resolved after drugs stopped. Pancreatitis is a rare labeled adverse event.

Unlabeled adverse events underlined
Source: Adverse Event Reporting System, FDA

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Serious Adverse Events (continued)

Respiratory Disorders (n=4)

Two cases with temporal relationship, one with a positive re-challenge.

- 3 month old premature infant (28 wks) with fistula secondary to short gut syndrome. Became hypoxic after 1 dose octreotide (1.8 mcg administered as 9mcg/mL over 30 minutes). Re-challenged with lower concentration (7mcg/mL over 30 minutes). Repeated hypoxia.
- 2 year old male with HIV associated diarrhea, AIDS, CHF and numerous other medical problems on octreotide SC or intravenously x 2 mos stopped breathing after a 50 mcg IV dose over 1 minute. Patient recovered with oxygen.

Unlabeled adverse events underlined
Source: Adverse Event Reporting System, FDA

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Serious Adverse Events (continued)

Respiratory Disorders (continued)

Two cases are difficult to assess due to underlying conditions.

- 6 month old premature (24 wks) infant with bronchopulmonary dysplasia s/p NEC on octreotide for fistula had multiple episodes of hypoxia. Developed severe pulmonary HTN. Discharged home on oxygen.
- 11 month old with history of GI motility problem, and other unknown medical history. On octreotide for 2 mos, developed cataracts, pneumonia, and persistent hypoxia.

Unlabeled adverse events underlined
Source: Adverse Event Reporting System, FDA

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Serious Adverse Events (Continued)

Cardiac Disorders (n=4)

Two cases with bradycardia which is a labeled event

- 13 year old male with cranial hemorrhage 2º to arteriovenous malformation and chylothorax developed sinus bradycardia to 42 during a 220 mcg octreotide infusion (72 mcg had been administered). Resolved minutes after infusion stopped.
- 11 year old male with bradycardia to 40 during 120 mcg octreotide infusion for gastric ulcer bleed . Successfully treated with atropine. Limited information provided.

Unlabeled adverse events underlined
Source: Adverse Event Reporting System, FDA

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Serious Adverse Events (Continued)

Cardiac Disorders (continued)

Two cases which are difficult to assess due to concomitant medication and insufficient information

- 15 year old male with Noonan Syndrome developed sudden chest tightness and pain. BP and "other observations normal". Patient on Celebrex.
- 8 month old male with <u>eosinophilia</u>, dysrhythmia, palpitations and "heart rate change" with octreotide. Treated with defibrillation and drug cardioconversion. No additional information.

Unlabeled adverse events underlined
Source: Adverse Event Reporting System, FDA

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Serious Adverse Events (Continued)

Nervous System Disorders (n=3)

All cases difficult to assess due to underlying condition or insufficient information

- 12 year old female with pituitary macroadenoma with acute onset of diabetes insipidus and bilateral cavernous sinus syndrome one day after start of octreotide. Improved after switched to Sandostatin® LAR Depot.
- 16 year old with Gardner's syndrome and short bowel syndrome and fistula on octreotide for 6 months. Hospitalized with encephalopathy. Possible interferon neurotoxicity.
- 19 day old male with hyperinsulinism experienced lethargy after given octreotide SC. Octreotide discontinued.

Unlabeled adverse events underlined
Source: Adverse Event Reporting System, FDA

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Serious Adverse Events (Continued)

Metabolism and Nutrition Disorders (n=3)

All cases difficult to assess due to concomitant treatment or insufficient information

- 2 ½ year old female with autoimmune gastroenteropathy on Total Parental Nutrition (TPN) with hyponatremia, hypokalemia and hypomagnesemia while on octreotide.
- 16 year old female with acromegaly on octreotide x 1.5 years developed hypopituitarism after radiotherapy
- 12 year old male with hereditary pancreatitis on octreotide for acute pancreatitis. Next day experienced hyponatremia. Causality described as remote by reporter.

Unlabeled adverse events underlined
Source: Adverse Event Reporting System, FDA

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Serious Adverse Events (Continued)

General Disorders (n=3)

All cases difficult to assess due to underlying condition or insufficient information

- 18 month old female given incorrect drug concentration resulting in under dosage. No information on intervention.
- 15 month old female with fever. Diagnosed with Klebsiella sepsis after multiple work-ups. Resolved 10 days after med stopped.
- 14 month old with fever after 4 months on drug. No change with discontinuation.

Unlabeled adverse events underlined
Source: Adverse Event Reporting System, FDA

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Serious Adverse Events (Continued)

Infections (n=2)

All cases difficult to assess due to underlying condition

- Newborn with hypoglycemia on octreotide x 6 days developed sepsis, lethargy and elevated GGT and Alk Phos. Sepsis successfully treated with antibiotics. Octreotide-weaned, LFTs improved.
- 20 day old male with congenital nesidioblastoma experienced sepsis, tachycardia, edema, fever and vasodilation 12 hours after receiving Sandostatin LAR® Depot.

Unlabeled adverse events underlined
Source: Adverse Event Reporting System, FDA

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Serious Adverse Events (Continued)

Laboratory measurements (n=1)

- 1year old female on octreotide for GI hemorrhage developed CPK to 10,000. No other information. Case difficult to assess due to insufficient information.

Psychiatric Disorders (n=1)

- 16 year old female with pituitary macroadenoma on octreotide after surgery and radiotherapy who exhibited signs of dependency with craving and self increased dose from 900 mcg daily to 1800 mcg daily. Improved with weaning over 4 weeks. Labeling states no indication that octreotide has potential for dependency.

Unlabeled adverse events underlined
Source: Adverse Event Reporting System, FDA

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Serious Adverse Events (Continued)

Blood Disorders (n=1)

- 12 year old male with injury to liver and pancreas after traffic accident experienced thrombotic microangiopathy after octreotide x 1 day. Improved after octreotide discontinued. Case difficult to assess due to underlying condition.

Pregnancy (n=1)

- 43 year old mother on octreotide for hypophysis macroedema delivered premature infant (gestation unknown) with respiratory insufficiency. Discharged home. Case difficult to assess due to insufficient information.

Unlabeled adverse events underlined
Source: Adverse Event Reporting System, FDA

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Published Pediatric Case Reports

- Premature female (33 weeks) infant with hyperinsulinism on octreotide (beginning with 6 mcg/kg/day increased to 40 mcg/kg/day) for 5 weeks. Developed cholestatic jaundice and cholelithiasis. Patient improved with decrease in octreotide to 6 mcg/kg/day and treatment with ursodeoxycholic acid.

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Pediatric Deaths Since Market Approval

10/21/1988 – 2/12/2007

- 11 (4 US) unduplicated cases
  - 1 case during the post-exclusivity period
  - 10 cases prior to the post-exclusivity period

Reported Uses of Octreotide

- Chylothorax (3)
- Fistula (2)
- Hemorrhage (1)
- Diarrhea (1)
- Hyperinsulinism (1)
- Unknown use (3)

Source: Adverse Event Reporting System, FDA

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Deaths Since Market Approval

Gastrointestinal Disorders (n=4)

- 16 day old on octreotide (titrated to 25 mcg subcutaneous every 6 hours) for hyperinsulinism developed clinical signs of NEC after 6 days. During surgery, patient found to have extensive NEC. Patient died 2 hours later.
- 1 month old female with Transposition of the Great Arteries post surgical repair on octreotide (titrated to 8 mcg/kg/hr) developed abdominal distension and atrial thrombus after 1 week. Patient died from NEC, sepsis, respiratory failure, and hepatic necrosis. No thrombus noted on autopsy.

Unlabeled adverse events underlined
Source: Adverse Event Reporting System, FDA

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Necrotizing Enterocolitis (NEC)

- Incidence
  - Population-Based
    - 0.5 – 5 per 1000 live births (all)
      - ~ 90% cases pre-term (~6-7% NEC VLBW <1500 grams)
    - 0.05 – 0.4 per 1000 live births (term neonates >37 wks. GA)
      - 2/3 with congenital diseases (e.g., CHD, endocrine)
  - 3.3% CICU Admissions (indep. surgery) 7.6% HLHS
    - Risk Factors: HLHS/Truncus/AP window; younger GA, episodes of low output/shock.

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Necrotizing Enterocolitis (NEC)

- Pathophysiology “poorly understood”
  - Factors: Impaired motility, hypoxic-ischemic injury, breakdown epithelial barrier, abnormal bacterial colonization, immature or abnormal inflammatory response.
- Overall Mortality (all NEC): 15 – 35%
- 20 - 40% require surgery, with 50% mortality

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Off-Label Uses of Octreotide in Neonate

- Chylothorax (after failure conservative mgmt.)
  - Primary: congenital
  - Secondary: traumatic or obstructive (thoracic duct, SVC)
  - Risks: immunodeficiency, malnutrition, electrolyte disturbances
- Octreotide Dosing and Reported Experience
  - Dose: IV 0.3 – 10 micrograms/kg/hour
  - Duration: 3 – 27 days
  - Regimen: IV infusion (sc, IV bolus)
  - Resolution: 3 to 15 days (usually 5 – 6 days)
  - Reported Patients: N ~ 65

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Off-Label Uses of Octreotide in Neonate

- Congenital Hyperinsulinism
  - Octreotide suppresses calcium-mediated insulin release
  - useful in short-term management of hypoglycemia
  - due to tachyphylaxis, octreotide effective as chronic treatment in only limited number of infants with severe hyperinsulinism
- Octreotide Dosing
  - Starting doses: 1 to 10 micrograms/kg/day either subcutaneously in three to four doses or by continuous intravenous infusion
  - Doses as high as 40 micrograms/kg/day have been used in infants and children.

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Deaths Since Market Approval

Gastrointestinal Disorders (continued)

Cases difficult to assess due to underlying condition or concomitant medication

- 15 year old male with dyskeratosis congenita (post stem-cell transplant with graft vs. host disease). On octreotide (titrated to 20 mcg/kg/hr) for diarrhea. 1 week later, developed severe hypotension, respiratory distress, and abdominal pain with septic shock. Died 10 days later from diffuse hemorrhagic necrosis of the GI system and diffuse capillaritis of the brain and gut.
- 3 year old with nephrotic syndrome on prednisone. 1 day after the start of octreotide (dose and indication unknown) the patient developed a bleeding duodenal ulcer and died that day.

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Unlabeled adverse events underlined
Source: Adverse Event Reporting System, FDA

Deaths Since Market Approval

Respiratory Disorders (n=1)

Case is difficult to assess due to underlying condition.

- 3 week old premature male (29 wks) with history of NEC on octreotide (titrated to 3 mcg/kg/hr) for a fistula. Patient developed hypoxia and mild pulmonary hypertension. Improved with discontinuation. Died at 6 months from liver and renal failure 2^{o} short bowel syndrome.

Unlabeled adverse events underlined
Source: Adverse Event Reporting System, FDA

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Deaths Since Market Approval

Cardiac Disorders (n=2)

Case is difficult to assess due to underlying condition

- 1 year old male with intermittent 2^{0} AV block (Mobitz) treated with octreotide (titrated to 60 mcg daily subcutaneously). Improved after discontinuation. Patient died several months later from underlying cardiac and metabolic storage disease.

Case was reported during the post-exclusivity period.

- 4 month old with Noonan's syndrome on octreotide (titrated to 18 mcg/kg/hr). 2 weeks later developed abdominal distension and hypoglycemia after octreotide stopped. Patient died a few days later from cardiac arrest after pneumothorax, anuria and hypoglycemia.

Unlabeled adverse events underlined
Source: Adverse Event Reporting System, FDA

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Deaths Since Market Approval

Hepatobiliary Disorders (n=3)

Cases difficult to assess due to underlying conditions

- 7 month old with abnormal GI motility and elevated LFTs. On chronic TPN. Bilirubin and liver enzymes increased further on octreotide (6 mcg every 6 hours IV) and erythromycin for unknown indication (TSB 31-37.9; D. Bili 20.9-22.6). Patient died of hepatic failure 5 days later.
- 9 year old female s/p repeat liver transplantation on octreotide (1.5 mg daily IV) for an unspecified hemorrhage. Also presented with hepatitis. Patient died (date and cause of death unknown)

Unlabeled adverse events underlined
Source: Adverse Event Reporting System, FDA

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Deaths Since Market Approval

Miscellaneous Disorders (n=2)

Cases difficult to assess due to underlying condition

- 6 year old male with leukemia who experienced a deterioration in his condition after starting octreotide (unknown dose and indication) and cyclosporine. Patient died 1 year later. Cause of death unknown.
- 16 month old male s/p colectomy developed fever and intestinal obstruction 8 hours after a single dose of 100 mcg of octreotide subcutaneously. Patient died of multi-system organ failure and possible intracranial hemorrhage.

Unlabeled adverse events underlined
Source: Adverse Event Reporting System, FDA

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Use of Octreotide in Infants

- Octreotide is used for a variety of unapproved indications
- Despite the lack of controlled trial data, off-label use of octreotide in the pediatric population is published widely
- Almost 50% of pediatric reports occurred in children < 2 years (24/52 = 46%)

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Use of Octreotide in Infants

- Majority of deaths occurred in children < 2 years (7/11 = 64%)
- A wide range of octreotide doses are used in the pediatric population. Sandostatin® injection is used in the majority of cases.
- Continuous infusion used in 6 cases: Not an approved method of administration in any population for any indication.

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Summary: Octreotide

- Adverse events seen with octreotide are serious and not limited to a particular System Organ Class.
  - There is a potential temporal relationship since 27% of the reported adverse events occurred within 24 hours of starting octreotide.

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Summary: Octreotide

- Since market approval there have been 36 reports of serious adverse events (25 non-fatal and 11 deaths).
- Most cases are difficult to assess due to underlying condition, concomitant medication or insufficient information.

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Summary: Octreotide

8 cases are possibly related to octreotide use

- 3 reports of necrotizing enterocolitis
- 1 report of repeated episodes of hypoxia and 1 report of repeated hypoxia with re-challenge.
- 1 report of pancreatitis (labeled)
- 2 reports of bradycardia (labeled)

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Unlabeled adverse events underlined
Source: Adverse Event Reporting System, FDA

Summary: Octreotide

- Almost 50% of reports were in children < 2 years using Sandostatin® injection
- The majority of deaths were in children < 2 years
  - Overall, there was no discernable trend between pediatric octreotide use and reports of death
- This completes the one-year post-exclusivity adverse event reporting as mandated by BPCA.

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Sandostatin® Injection Labeling Pediatric Use Section

- No formal controlled clinical efficacy and safety studies
- Description of efficacy and safety data derived from literature reports pertaining to use in 49 neonates and infants with congenital hyperinsulinism
  - Doses used (3-40 mcg/kg/day)
  - Efficacy (avoidance of surgery)

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Sandostatin® Injection Labeling Pediatric Use Section

- Description of safety data from literature reports
  - Safety (short term)
    - Diarrhea
    - Steatorrhea
    - Vomiting
    - Abdominal distension
  - Safety (long-term)
    - Poor growth
    - Poor weight gain
    - gallstones

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Questions for the Pediatric Advisory Committee

- Do you recommend changes to the labeling?
  - Pediatric Use section (additions or deletions)
  - Updating the labeling to include information presented on post-marketing adverse events
- How can this information be disseminated outside of the labeling?

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