

Follow Up Adverse Event Review: Octreotide

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Background 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 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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Pediatric Exclusivity Studies: 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. (Efficacy not demonstrated)
- A six-month open label extension study
- Safety results; higher incidence of new cholelithiasis

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Summary of AE Reporting to PAC in April 2007

- In April 2007, since market approval in 1988, there were 36 reports of serious adverse events (25 non-fatal and 11 deaths).
- 8 cases were possibly related to octreotide use
 - 3 reports of necrotizing enterocolitis (unlabeled)
 - 1 report of repeated episodes of hypoxia and 1 report of repeated hypoxia with re-challenge (unlabeled)
 - 1 report of pancreatitis (labeled)
 - 2 reports of bradycardia (labeled)

Source: Adverse Event Reporting System, FDA

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April 2007 PAC

Recommendations/Comments

FDA should:

- Place information in labeling concerning the occurrence of adverse events in infants
 - Some noted that information in the labeling should not imply that a causal link was established
- Consider ways to disseminate information to healthcare providers

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April 2007 PAC

Recommendations/Comments continued

FDA should:

- Consider improving consistency between Sandostatin[®] LAR and Injection labeling
 - include the negative exclusivity study results in the Sandostatin[®] Injection labeling
- Provide a 1 year update focused on observed post marketing adverse events of necrotizing enterocolitis and hypoxia

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Adverse Event Reports February 2007 to May 2008

Crude counts of Octreotide Reports (US counts in parentheses) ¹ Source: AERS, Reports Received Between 12 Feb 2007 (cutoff date for previous OSE review) and May 22, 2008			
	All reports (US)	Serious ² (US)	Deaths (US)
Adults (≥ 17 yrs.)	123(44)	119(43)	17(5)
Pediatrics (0-16 yrs.)	10(0)	10(0)	1(0)
Age unknown (Null values)	50(14)	49(13)	8(1)
Total	183(58)	178(56)	25(6)

¹May include duplicates
²Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, and congenital anomaly.

Adverse Event Reports February 2007 to May 2008 (N=10)

Characteristics of Cases:

- 50% less than 2 years old
- Formulation
 - 6 cases – Sandostatin[®] Injection
 - 2 cases – Sandostatin LAR[®]
 - 2 cases – unknown formulation

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Adverse Event Reports February 2007 to May 2008 (N=10)

Off-Label Uses:

- Chylothorax (4)
- Hypoglycemia/hyperinsulinism (2)
- Insulinoma (1)
- Pituitary Adenoma/Gigantism (1)
- Diarrhea (1)
- In utero exposure (1)

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Adverse Event Reports February 2007 to May 2008 (N=10)

Deaths (n=1)

Neonate born with multiple congenital anomalies (microcephaly retromicrognathia, hypertelorism) as well as hypotonia and mild tachypnea. Placed on Sandostatin[®] Injection (0.3mg every 8 hours) for insulinoma 2 days after birth. Patient died 1 month later. Cause of death not reported.

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Adverse Event Reports February 2007 to May 2008 (N=10)

Necrotizing enterocolitis (n=1)

- 2 month old with history of prematurity, congenital heart disease, and refractory chylothorax on multiple medications. Patient received three courses of octreotide. During one of the first two courses (unknown dose), the patient developed necrotizing enterocolitis. After two days on the third course of octreotide (10µg, unknown frequency), the patient developed bloody stools, bowel dysfunction, and necrotizing enterocolitis. Outcome unknown.

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Adverse Event Reports February 2007 to May 2008 (N=10)

There were no new reports of hypoxia

Other adverse event reports (n=8):

- Hyperglycemia
- Hypoglycemia (in-utero exposure)
- Hypoglycemia (neonatal exposure)
- Bradycardia and transient cardiac arrest
- Hypotension
- Fluid retention and metabolic acidosis
- Osteonecrosis of the femoral head
- Persistent effusion (loss of efficacy)

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Labeling Changes

Sandostatin® LAR

- labeling was changed to remove discussion of use of octreotide for congenital hyperinsulinism (March 2008)

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Summary

- An additional 10 reports of serious adverse events including one report of necrotizing enterocolitis were received
- One approach FDA is considering is to:
 - revise labeling to clarify there are no approved pediatric indications
 - remove the description of the 49 published case reports from the Sandostatin Injection labeling
- FDA will continue its standard, ongoing safety monitoring for octreotide.

Does the Advisory Committee concur with the above stated approach?

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