# EP-711
# Parenteral Somatostatin Analogs: A Focus on Injection-site Adverse Reactions

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*Potential conflict of interest may exist.

## ABSTRACT

**Background:** Injectable somatostatin analogs are the standard medical treatment for acromegaly. Injection-site adverse reactions (ADRs) reported for parenteral somatostatin analogs were examined in the literature or in the U.S. Food and Drug Administration (FDA) Adverse Events Reporting System (AERS), in parallel to those reported in the respective drug labels.

**Methods:** PubMed was searched using the following criteria: Period: 1995-2013; Drugs: octreotide (Sandostatin®), lanreotide (Somatuline®), or somatostatin analogs; ADRs of interest.

FDA AERS files were reviewed for the period from Q1 2004 to Q1 2014. ADRs reported in patients treated with somatostatin analogs were extracted as follows: (i) Drugs: octreotide, (Sandostatin®), lanreotide (Somatuline®), (ii) somatostatin analogs were the primary or secondary suspected drug, and (iii) preferred terms (MedDRA) containing keywords injection, application, or administration site.

**Results:** Literature data showed injection-site pain in up to 76% of patients and nodules in up to 67% of patients. The Sandostatin LAR® label describes injection-site pain in up to 11% of acromegaly patients and in up to 50% of patients with neuroendocrine tumors. The Somatuline® label reports injection-site reactions (pain, mass, induration, nodules, and pruritus) in 9%. In the AERS database, the most frequent injection-site ADRs reported were injection-site pain (306 cases), mass (85), hemorrhage (74), swelling (40), induration (29), discomfort, erythema (28), nodule (27), hematoma (17), pruritus (16), abscess (12), inflammation (12), scar (10), and bruising (10). Events reported in AERS increased annually from 10 in 2004 to 236 in 2012, with a total of 841 events in 541 cases by Q1 2014.

**Conclusions:** The range of injection-site ADRs in both the literature and the FDA AERS database is wider than that reported in the somatostatin analog labels and includes ADRs of significant concern. As no Weber effect was demonstrated with the use of SRLs following approval, the reported adverse events were likely clinically significant. Because of the nature of reported injection-site ADRs and their physical burden, an oral alternative to chronic parenteral somatostatin injections could significantly benefit patient care.

## INTRODUCTION

- The somatostatin receptor ligands (SRLs), octreotide (Sandostatin®), and lanreotide (Somatuline®), are approved by the U.S. Food and Drug Administration (FDA) for the treatment of acromegaly and certain neuroendocrine tumors.
- These peptide agents must be given parenterally through intramuscular or deep subcutaneous injections and their administration is associated with significant injection-site adverse drug reactions (ADRs).
- The reported incidence and nature of these ADRs vary considerably, with the product labeling citing injection-site pain and other reactions in up to 50% of patients[1-3]; a recent acromegaly patient survey reports injection-site pain in 70% of patients, and nodules, swelling, and bruising in 38%, 28%, and 16% of patients, respectively.[4]

## OBJECTIVE

- The purpose of this study was to compare the incidence and nature of SRL-associated injection-site ADRs reported in the published literature, the product labeling of currently available SRLs, and the FDA Adverse Events Reporting System (AERS) database.

## METHODS

- To assess the incidence and nature of SRL-associated injection-site ADRs reported in the literature, a PubMed search was conducted using the following criteria:
  - Time period: 1995-2013
  - Types of articles: clinical studies, reviews, case reports, position papers
  - Drugs: Octreotide (Sandostatin), lanreotide (Somatuline), somatostatin analogs
  - ADRs of interest: injection-site reaction, skin reaction, granuloma, nodule, lipoatrophy
- The most current product labeling for the available immediate-release and long-acting octreotide and lanreotide formulations was examined for reported incidence of injection-site ADRs.
- The FDA AERS quarterly files available to the public from Q1 2004 to Q1 2014 were reviewed.[5] The AERS database contains information on adverse events and medication error reports submitted to the FDA by healthcare professionals, consumers, and drug manufacturers. Adverse events reported in patients treated with SRLs were extracted from the AERS database as follows:
  - Drug selection keywords used were octreotide, Sandostatin, lanreotide, and Somatuline
  - Only adverse event reports in which an SRL was the primary or secondary suspected drug were selected
  - For the suspected relevant drugs, only adverse event preferred terms from Medical Dictionary for Regulatory Activities (MedDRA), including the keywords injection site, application site, and administration site, were selected

## RESULTS

### Injection-Site Reactions Reported in the Literature

- Based on the search criteria, 21 articles were reviewed, including larger comparative studies and case reports. Injection-site pain was reported in up to 76% of patients treated with long-acting octreotide, and nodules were reported in up to 67% of patients receiving octreotide or lanreotide injections.Other reactions reported in case studies include ulcers, fat necrosis, granuloma formation, and lipoatrophy.
- Alexopoulou and colleagues (2004) examined the efficacy and tolerability of Somatuline Autogel therapy in 25 acromegaly patients previously treated with Sandostatin LAR. Mild to moderate pain at the injection site was reported by 76% of the patients for Sandostatin LAR and 12% of patients treated with Somatuline Autogel.[6]
- Salvatori and colleagues (2010) looked at injection site reactions in 33 patients treated with Sandostatin LAR who switched to Somatuline Autogel. 59.4% of patients on Sandostatin LAR reported that the injections are somewhat painful vs 43.8% of patients on Somatuline Autogel. Moderately painful injections were reported in 6.3% of patients in both groups and very painful injections were reported in 9.4% of patients on Sandostatin LAR only.[7]
- Data from the SODA study (Salvatori et al. 2013) show that 11 % (19/166) of patients treated with Somatuline found injections to be very/extremely painful, 55% (92/166) described them as mildly/moderately painful and only 33% (54/166) reported injections to be painless.[8]
- Surprisingly, the majority of patients in the SODA study on Somatuline still preferred to be injected by a trained nurse than self-inject or be injected by a family member - only 16% of the patients self-injected while 35% of patients received injections from healthcare professionals.[8]
- Large fat and skin necrosis, injection site granulomas, nodules or lipoatrophy are reported in various case reports (Rideout & Graham 2001[9]; Burman et al. 2010[10]; Debono et al. 2008[11]; Atmaca & Erbas 2005[12]).
- Adelman and colleagues (2012) have shown that Sandostatin LAR had a long administration time (5.5 minutes) with a 2.5% clogging rate.[13] Schweinsberg and colleagues (2011) described a similar experience with Sandostatin LAR.[14] Alexopoulou and colleagues (2004) noted that the preparation and administration of Sandostatin LAR is a complicated procedure involving multiple steps.[6]

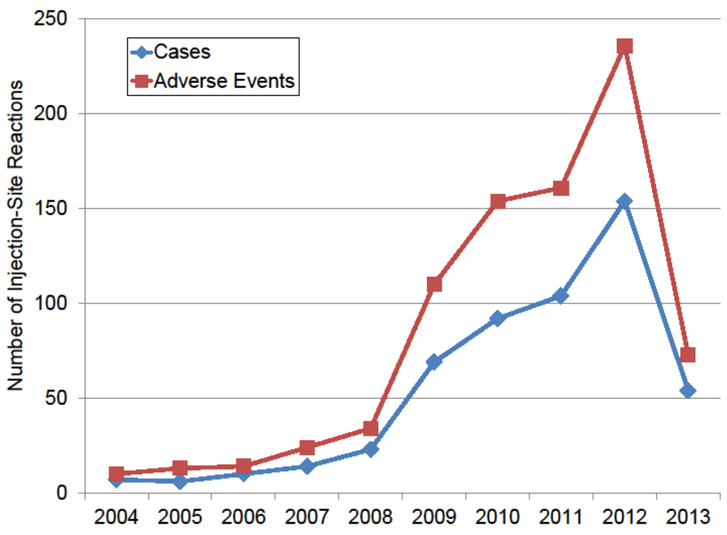
### Injection-Site Reactions Reported in Product Labeling

- In the product labeling for long-acting octreotide, injection-site pain is reported in 2%, 9%, and 11% of acromegaly patients receiving doses of 10 mg, 20 mg, and 30 mg, respectively. Among carcinoid patients, injection-site pain was reported in approximately 20% to 25% at the 10-mg dose and in approximately 30% to 50% at the 20-mg and 30-mg doses.[1]
- The labeling for immediate-release octreotide reports a 1% to 4% incidence of hematoma, bruising, and edema, and 7.7% incidence of pain with injection[2]
- In the product labeling for long-acting lanreotide, incidence of injection-site reactions, including pain, mass, induration, nodules, and pruritus, was 9%.[3]

### Injection-Site Reactions Reported in the FDA AERS Database

- A total of 841 injection-site ADRs in 541 cases suspected to be related to the administration of parenteral SRLs were reported to the FDA from 2004 to Q1 2014.
- Events reported in the AERS increased annually from 10 in 2004 and peaked to 236 in 2012 (**Figure 1**).[5]

**Figure 1. Annual Number of Injection-Site Reactions Reported for Parenteral SRLs in the FDA AERS Database, 2004-2013**




- In the AERS database, the most frequent injection-site reactions reported (**Table 2**) were injection-site pain, followed by injection-site mass, hemorrhage, reactions (not specified), swelling, induration, discomfort, erythema, nodules, and hematoma. Other events included pruritus, abscess, inflammation, scar, and bruising.
- Potentially nonreversible injection-site ADRs included injection-site mass, induration, discoloration, nodule, scar, calcification, and atrophy.

**Table 2. Most Frequent Injection-Site Reactions (≥10 events) Reported for Parenteral SRLs: FDA AERS Database, Q1 2004–Q1 2014**

| Injection-Site Reaction | n | % of Total (N=841) |
|---|---|---|
| Pain | 306 | 36.4 |
| Mass | 85 | 10.1 |
| Hemorrhage | 74 | 8.8 |
| Reactions (not specified) | 63 | 7.5 |
| Swelling | 40 | 4.8 |
| Induration | 29 | 3.4 |
| Discomfort | 28 | 3.3 |
| Erythema | 28 | 3.3 |
| Nodules | 27 | 3.2 |
| Hematoma | 17 | 2.0 |
| Pruritus | 16 | 1.9 |
| Abscess | 12 | 1.4 |
| Inflammation | 12 | 1.4 |
| Scar | 10 | 1.2 |
| Bruising | 10 | 1.2 |

- Injection-site ADRs of significant concern included abscess, inflammation, infection, necrosis, cellulitis, phlebitis, and ulcer.
- The absence of a Weber effect (i.e., increase in adverse event reporting in the first 2 years after approval followed by a rapid decline due to a reduction in the reporting of clinically mild or trivial reactions)[15] suggests that the reported reactions were clinically significant.

## STUDY LIMITATIONS

- The percentage of patients treated with parenteral SRLs who experience injection-site ADRs cannot be inferred from the FDA AERS database, nor can the relative frequency of these reactions in clinical practice.

## CONCLUSIONS

- The spectrum of injection-site ADRs in the literature and the FDA AERS database is wider than that reported in the product labeling of commercially available SRLs.
- Some ADRs reported to the FDA were of significant concern, including injection-site abscess, inflammation, infection, necrosis, cellulitis, phlebitis, and ulcer.
- The range of injection-site ADRs associated with parenteral SRLs and their potential burden underscore the benefit that an oral octreotide formulation may provide for patients.

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### Disclosures

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