Neuroendocrine Tumors and Lanreotide Depot: Clinical Considerations and Nurse and Patient Preferences

Pamela Ryan, RN, BSN, Alexandria T. Phan, MD, Daphne T. Adelman, RN, BSN, MBA, and Michiko Iwasaki, RN, CCRC

Background: Somatostatin analogs (SSAs) are a mainstay therapy for the treatment of carcinoid syndrome associated with neuroendocrine tumors (NETs). They are effective for a range of gastroenteropancreatic NETs (GEP-NETs). Lanreotide depot (Somatuline®) is an SSA that is approved for the treatment of GEP-NETs to improve progression-free survival (PFS).

Objectives: The article reviews the efficacy, safety, and administration of lanreotide depot and relates those attributes to considerations and preferences of oncology nurses and their patients.

Methods: A review of the literature on the use of lanreotide for the treatment of NETs and carcinoid syndrome was conducted. In addition, the literature on drug delivery and routes of administration was surveyed to provide context for comparative studies related to clinical and patient preferences.

Findings: Lanreotide depot prolongs PFS and is well tolerated by patients who expressed satisfaction in the ability to control symptoms related to carcinoid syndrome. Nurses cited several benefits to using lanreotide depot in the clinical setting, including more time saved to address other patient care issues. Attributes of lanreotide depot—including its efficacy, safety and tolerability, dosing and administration, and cost—may contribute to healthcare decisions regarding the treatment and management of NETs.

Neuroendocrine tumors (NETs) arise from secretory cells of the neuroendocrine system and are predominantly found in the gastrointestinal tract and pancreas, although they can occur in virtually every organ (Gives & Strosberg, 2014). The incidence of NETs may be as high as 5.86 in 100,000 (95% confidence interval [CI] 5.4, 6.35), based on 2009 data (Hallet et al., 2014). Advanced metastatic NETs are associated with a relatively poor prognosis and may be unresectable. Treatment has traditionally focused on management of the symptoms of this chronic condition (Caplin, Pavel, et al., 2014; Oberg, 2012; Wolin, 2012).

Patients who present with well-differentiated (low and intermediate grade) NETs of the stomach, intestine, and pancreas are usually first treated with surgical resection whenever possible and/or ablation. Medical management for gastroenteropancreatic (GEP)-NETs may also involve chemotherapeutic agents, monoclonal antibodies, and/or biotherapy with somatostatin analogs (SSAs) (Falconi et al., 2012; Kulke et al., 2010; National Comprehensive Cancer Network [NCCN], 2015; Oberg, 2012). Long-acting SSAs have been used successfully to treat GEP-NETs (Caplin, Pavel, et al., 2014; NCCN, 2015). Generally well tolerated, SSAs are used for the relief of symptoms associated with carcinoid syndrome, a condition that typically presents in advanced neuroendocrine cancer that has metastasized to the liver or with secretory pancreatic or midgut NETs (Pavel et al., 2012).

This article reviews a long-acting SSA, lanreotide depot (Somatuline®), and examines factors such as efficacy, tolerability, dosing and administration, patient and nurse preferences,
and payor considerations that may affect clinical decision-making. A PubMed search using the terms lanreotide and neuroendocrine tumors was used to identify clinical data relevant to this review. In addition to the literature on antitumor effect, a separate search on injection technique and preferences was carried out.

Lanreotide Depot

Indications

Lanreotide depot is indicated for unresectable, well- or moderately differentiated, locally advanced or metastatic GEP-NETS to improve PFS (Ipsen Biopharmaceuticals, 2015). Lanreotide depot also is included in the NCCN guidelines as a treatment option for nonresectable, primary nonmetastatic, and distant metastatic carcinoid tumors and pancreatic NETs as well as for low- and intermediate-grade lung NETs (NCCN, 2015). Lanreotide depot also is indicated in the United States and Europe for long-term treatment of acromegaly in patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy, and in Europe for the relief of symptoms associated with GEP-NETS (Ipsen Biopharmaceuticals, 2015; Kyriakakis, Chau, Lynch, Orme, & Murray, 2014).

Formulation and Pharmacokinetics

Lanreotide is an analog of human somatostatin, and lanreotide depot is the first marketed sustained-release formulation produced via peptide self-assembly, an intrinsic biophysical property that creates a highly stable form of the active drug (Valery et al., 2004). This semi-solid gel is an innovation of the long-acting microsphere-based formulation of lanreotide and comprised of the drug plus water without additional excipients or polymers. Long-acting lanreotide depot is supplied as a powder for suspension and intramuscular injection and intended for dosing every 7, 10, or 14 days (Ipsen Biopharmaceuticals, 2015). Although the microsphere-based formulations of SSAs have been shown to be effective, they have inherent disadvantages, including the need for reconstitution before injection and potential burst release of the drug. In addition, microsphere-based formulations often necessitate potentially painful intramuscular injections, as well as large injection volumes that can limit the amount of drug administered at a time and, therefore, the length of drug exposure (Lewis & Illum, 2010; Plourde et al., 2005; Zaybak, Gunes, Tamsel, Khorshid, & Eser, 2007).

The semi-solid gel formulation is provided as a single-use, prefilled delivery system for once-monthly deep subcutaneous injection. Upon injection, lanreotide forms a depot at the injection site and rapidly reaches its highest levels in plasma, as shown in a study of healthy volunteer participants (Antoni-joyan et al., 2004). This property may eliminate the need for a short-acting SSA at initiation of treatment. The therapeutic concentration is reached on day 1 and remains in therapeutic range during the 28-day dosing interval, with minimal peak-to-trough fluctuations. Specifically, the depot provides controlled, sustained release of the drug for an extended period of time with low peak serum concentration ($C_{\text{max}} = 6.79$ ng/ml), a long terminal half life (30.1 days), and a mean serum concentration of 1.69 ng/ml four weeks after injection (Ipsen Biopharmaceuticals, 2015). In patients with GEP-NETs who received a 120 mg dose of lanreotide depot every four weeks, steady-state concentrations were reached after four to five cycles, and the mean trough serum lanreotide concentrations at steady state were 5.3–8.6 ng/ml (Ipsen Biopharmaceuticals, 2015). The pharmacokinetic properties of lanreotide depot formulation render it suitable for a once-monthly dosing interval. The release profile of the drug during the dosing period is unique; therefore, no known dose equivalence exists with other SSAs for 120 mg lanreotide depot.

Efficacy and Safety Studies of Antitumor Activity

The CLARINET study of long-acting lanreotide depot was the first placebo-controlled clinical trial in GEP-NETS to use PFS as a primary endpoint. This phase III, 96-week, randomized, double-blind, placebo-controlled, international, multicenter study enrolled 204 adult patients with well- or moderately differentiated, metastatic and/or locally advanced unresectable GEP-NETS and Ki67 less than 10%. Patients were randomly assigned to receive lanreotide depot (120 mg subcutaneous) ($n = 101$) or placebo ($n = 103$) once every 28 days. The median drug-exposure time for patients in the lanreotide depot group was 24 months (range = 1–25.3) compared to 15 months (range = 1–25.2) for the placebo group. PFS was assessed according to the Response Evaluation Criteria in Solid Tumors ((RECIST), version 1.0 (Therasse et al., 2000). Based on a hazard ratio (HR) of 0.47 (95% CI [0.3, 0.73]) for the primary endpoint of progression-free survival, the risk of disease progression within 96 weeks after the initial dose of lanreotide was reduced by 53% ($p = 0.0002$) in patients with metastatic GEP-NETS (Caplin, Pavel, et al., 2014; Caplin, Ruszniewski, et al., 2014). Treatment-related adverse events (AEs) occurred more frequently in the lanreotide depot group ($n = 50$) versus the placebo group ($n = 29$), and the majority of AEs were mild (17% in each group) or moderate (44% in the lanreotide depot group and 43% in the placebo group). Those patients from the core study were exposed to the study drug about 39 weeks longer than those in the placebo group, with the most common AE being diarrhea ($n = 26$ in patients treated with lanreotide depot compared with $n = 9$ for placebo). Serious AEs occurred in 25 patients who received lanreotide depot compared with 32 for the placebo group (Caplin, Pavel, et al., 2014). Serious AEs related to study treatment were hyperglycemia, diabetes mellitus, nausea, vomiting, abdominal pain, biliary fistula, and cholelithiasis in the lanreotide depot group and bile duct stenosis in the placebo group.

A multivariate analysis to identify prognostic factors for PFS in the CLARINET study indicated that treatment with lanreotide depot extended PFS across all patient subgroups and reduced the risk of progressive disease or death by 60% compared with placebo, adjusting for covariates. This risk was lowest among patients with no progressive disease at baseline. Among the factors evaluated for prognostic significance, hepatic tumor load—defined by tumor volume involving hepatic metastasis that is greater or less than a threshold of 25%—primary tumor type, and progressive
Management of Symptoms Associated With Carcinoid Syndrome

In addition to its activity as an antitumor agent, lanreotide depot is also used to manage symptoms associated with carcinoid syndrome (Poncet, Faucheron, & Walter, 2010). Short-acting SSA, administered subcutaneously as a bolus injection or via IV 1–4 times per day, is used as a rescue medication during initiation of treatment with long-acting SSAs to relieve breakthrough symptoms or to prevent carcinoid crisis, which is characterized by an acute episode of primary symptoms associated with carcinoid syndrome (e.g., prolonged flushing, diarrhea, abdominal cramps, cardiac complications). In a multinational phase III study of lanreotide depot in patients with GEP-NETs and carcinoid syndrome, lanreotide significantly reduced the need for rescue medication and showed a favorable safety/tolerability profile (Vinik, Wolin, Audry, Gomez-Panzani, & ELECT Study Group, 2014). That study included a 16-week placebo-controlled phase, followed by a 32-week open-label extension phase. For the first (double-blind) phase, patients who were naive to SSAs (n = 51, 44%) or had received prior treatment with another SSA (n = 64, 56%) were randomized to receive 120 mg of lanreotide depot (n = 59) or placebo (n = 56) once every four weeks. A novel primary endpoint, the mean percentage of days requiring rescue medication (MPDR), was selected owing to the inherent difficulty in assessing outcomes related to symptom control in carcinoid syndrome. The MPDR was lower in the lanreotide arm (34%, 95% CI [25, 42]) compared with the placebo arm (49%, 95% CI [40, 57]), and the absolute difference of 15% was statistically significant (p = 0.017) (five fewer days of rescue medication over the course of the assessment period from weeks 12 to 15). In addition, full or partial success, defined as three or fewer days using rescue medication per week, was significantly more common in the lanreotide depot group versus the placebo group (odds ratio = 2.4, 95% CI [1.1, 5.3], p = 0.04). The most common treatment-emergent AEs (TEAEs) in the lanreotide depot group compared with the placebo group were gastrointestinal-related AEs (n = 9, 16%, versus n = 5, 9%). Few TEAEs were deemed serious (n = 2, 3%, versus n = 5, 9%) or led to withdrawal (n = 1, 2% for each) for lanreotide depot and placebo, respectively (Vinik et al., 2014). Exploratory subanalysis of the population of patients in the ELECT study who had received treatment with long-acting or rescue SSA prior to randomization for treatment with lanreotide depot (n = 33) or placebo (n = 31) showed that the number of patients who had achieved control of carcinoid syndrome symptoms, defined as zero days of rescue short-acting SSA medication from weeks 12 to 15, was two times greater for the lanreotide depot group compared with the placebo group (52% versus 26%).

Patient-Reported Outcomes

Factors that affect health-related quality of life (HRQOL) and patient satisfaction are also important to consider. Ruszniewski et al. (2014) assessed patients’ experiences with the use of lanreotide depot for the management of symptoms associated with NETs, satisfaction among patients with GEP-NETs and carcinoid syndrome-related diarrhea treated with lanreotide depot, HRQOL using the European Organisation for the Research and Treatment of Cancer Quality of Life Core-30 (EORTC QLQ-C30) and QLQ-G.1.NET 21 surveys, and physician-reported changes in symptoms related
to carcinoid syndrome. The study enrolled 273 patients who had a mean time since diagnosis of 4.4 years. Mean treatment duration with lanreotide depot (median dose = 120 mg per month) was 21.7 (SD = 28.6) months. Most patients reported being “completely” or “rather” satisfied with their progress in controlling carcinoid syndrome-related diarrhea (76%, n = 203 of 268) and flushing (73%, n = 107 of 146) during treatment with lanreotide compared with baseline symptoms before treatment (Ruszniewski et al., 2014).

Figure 1 illustrates the proportion of patients who reported an impact on their daily activities or symptoms before and during treatment with lanreotide depot. Across each measure related to diarrhea, treatment with lanreotide depot was associated with better control of symptoms, a finding that was consistent with HRQOL scores. In the placebo-controlled CLARINET study of lanreotide depot, no significant differences in HRQOL measures were identified (Caplin, Ruszniewski, et al., 2014). In the smaller, single-arm phase II study of lanreotide depot in patients with advanced NETs and progressive disease, symptom control and HRQOL were generally stable, with a nonsignificant trend of improvement according to patients’ self-reported symptoms and assessments based on the EORTC QLQ-C30 scores. Among nine patients who were symptomatic for NET-related carcinoid syndrome at baseline, five patients achieved complete relief with lanreotide treatment and three developed new symptoms during the study (Martin-Richard et al., 2013).

Nurse Preferences

With SSAs, injection-device usability, safety, and speed of administration are important factors that improve quality and safety in clinical practice and enhance patient experience. Nurses from several hospital centers in Europe and the United States with at least three years’ experience injecting long-acting SSAs and who were following or injecting at least three patients per year (N = 77) participated in a study of delivery systems used to administer SSAs (Adelman, Burgess, & Davies, 2012). For this study, lanreotide depot was supplied as a single-use, ready-to-use, prefilled syringe for subcutaneous injection with safety features, such as a retractable needle guard to prevent accidental needle sticks and a low-volume dose that helps to ensure full dose delivery (see Figure 2). This depot device was compared with a long-acting SSA device system consisting of a vial containing the drug and a diluent-filled syringe for subcutaneous injection with safety features, such as a retractable needle guard to prevent accidental needle sticks and a low-volume dose that helps to ensure full dose delivery (see Figure 2). This depot device was compared with a long-acting SSA device system consisting of a vial containing the drug and a diluent-filled syringe for subcutaneous injection with safety features, such as a retractable needle guard to prevent accidental needle sticks and a low-volume dose that helps to ensure full dose delivery (see Figure 2). This depot device was compared with a long-acting SSA device system consisting of a vial containing the drug and a diluent-filled syringe for subcutaneous injection with safety features, such as a retractable needle guard to prevent accidental needle sticks and a low-volume dose that helps to ensure full dose delivery.
nurses as potentially saving time and resources. Confidence that a full dose was delivered, ease of administration, safety (including reduced risk of clogging and an automatic needle guard to reduce risk of sticks), and efficacy were the most important attributes identified (Adelman et al., 2012). Figure 3 shows the relative importance of each attribute and the relative assessment for each device.

Although this study did not evaluate the delivery systems directly in a clinical setting with patients and may be considered largely subjective, reliable and time-saving dose delivery would be expected to favorably affect clinical practice as well as to have health economics implications. To test this hypothesis, Marty, Roze, and Kurth (2012) conducted a study of cost savings that leveraged the preference data from the nurses’ opinion study in combination with 2010 healthcare economics and epidemiologic incidence data from three European countries—Germany, France, and the United Kingdom. Cost models compared the success of injection, determined by the number of clogging events, and the time for SSA injections administered by experienced nurses in the clinical setting together with mean annual cost per patient for the estimated number of patients with NETs or acromegaly eligible for SSA treatment. Only direct costs were included, and the cost of a clogging event accounted for the loss of the drug in the clogged device plus the requirement to use a second device. The models showed that the reduced risk of clogging was the biggest driver of cost savings and that more reliable, consistent administration resulted in cost savings that, when extrapolated to the overall patient population, suggested considerable savings for payors (Marty et al., 2012). These savings were about $20 million annually across the three countries in the study.

Several studies have explored clinical experiences with subcutaneous and intramuscular modalities of SSA injection. In particular, the amount of excess fat at the injection site for intramuscular administration using standard needle sizes may lead to inadequate or failed dose delivery in overweight and obese patients. The highest risk for a failed intramuscular injection is associated with gender (female) as well as weight (body mass index greater than 24.9) (Boyd et al., 2013; Burbidge, 2007; Chan et al., 2006; Palma & Strohfus, 2013; Zaybak et al., 2007). Because intended intramuscular injections may actually be inadvertently administered subcutaneously in a significant number of patients in a real-world clinical setting, the administered dose may lead to reduced efficacy compared with what was shown in clinical trials. In a study of 115 patients who were administered long-acting SSA via gluteal intramuscular injection by experienced clinical nurses, 38% of injections (125 of 328) that were intended to be intramuscular were, in fact, delivered subcutaneously. The success rate increased by 44% after instruction; however, 25% of injections were still considered failures after training (Boyd et al., 2013). Conversely, patients with too little body fat, such as patients with cachexia or anorexia, also may not receive proper or adequate dosing via intramuscular administration. Also, because the success of an injection is associated with better control of symptoms, as shown in patients with carcinoid syndrome treated with SSAs, the implications of variable dosing as a function of body mass or thickness of subcutaneous fat may be clinically significant. Of note, among potential prognostic factors identified in the multivariate analysis of the phase III clinical trial of lanreotide depot by the CLARINET study group was an association of heightened risk of progressive disease and death for patients with below-median body mass index (36%) compared with above-median body mass index (HR = 0.64, 95% CI [0.41, 1], p = 0.0483) (Wolin et al., 2015). Although this was not a statistically robust demonstration of an association and additional studies are required, consistent and accurate dose administration is critical in the context of such potential risk.

Studies related to the inhibition of tumor growth by an SSA administered intramuscularly in relation to injection success and in situ pharmacokinetics have not been reported. However, a study of healthy volunteers (N = 42) documented pharmacokinetic differences between lanreotide depot delivered subcutaneously and intramuscularly. Although mean concentration time profiles of lanreotide depot were comparable for both routes of administration, area-under-the-curve measures were slightly lower during the late phase of the observation period for the patients whose doses were administered subcutaneously compared with those administered intramuscularly. The increased availability of drug in the late-release phase suggests a better long-term release profile with subcutaneous injection (Manon et al., 2015).

In addition to a potential impact on efficacious dose delivery, injection site and method may produce differences in

---

**Implications for Practice**

- Improve patient quality of life by becoming familiar with how once-monthly somatostatin analogs (SSAs) may reduce the amount of short-acting SSA rescue medications needed to treat the symptoms of carcinoid syndrome associated with neuroendocrine tumors (NETs).
- Understand the unique attributes of lanreotide in the management of patients with NETs, based on high level of evidence-based anti-tumor efficacy.
- Identify advantages for patient and nurses to using subcutaneous treatment with prefilled syringes, possibly reducing the failed dosing seen with intramuscular SSA administration that causes patient and nurse burden.

---

**How injected:** Deep subcutaneous

**How supplied and dose strengths:** Single-use, prefilled syringes of 60 mg, 90 mg, or 120 mg dose strength

**Needle length:** 0.79 inches (20 mm)

**Safety technology:** Incorporates Safe’n’Sound® syringe technology, including a retractable needle guard that prevents needle sticks

**Reconstitution:** Ready to use; no reconstitution or mixing is required

**Dose volume:** 0.5 ml (no measuring of dose is required)

**FIGURE 2. Lanreotide Depot Device**

*Note: Based on information from Ipsen Biopharmaceuticals, 2015.*
incidence of related AEs. Injection site reactions, including erythema, pain, and swelling, were observed less frequently with lanreotide depot subcutaneous injection compared with long-acting SSA via intramuscular injection ($p < 0.001$). This translated to an expressed preference for lanreotide depot injection compared with the other formulation in a majority of patients (17 of 25 compared with 2 of 25). Alexopoulou et al. (2004) also reported technical difficulties with injection administration with 40% of traditional intramuscular devices versus no reported technical problems with lanreotide depot injections ($p < 0.001$).

**Implications for Nursing**

The importance of oncology nurses to the overall treatment and management of GEP-NETs is reflected in several aspects of the disease management. First, most patients initially present with vague symptoms, such as weight loss, bleeding, or abdominal pain, and often are diagnosed incidentally with advanced disease, despite advances in imaging and biomarker assessments (Modlin, Moss, Chung, Jensen, & Snyderwine, 2008; Oberg, 2012). Delayed diagnosis means that oncology nurses are more likely to encounter patients

![Preference Scale](image)

**FIGURE 3. Nurse Evaluation of Lanreotide Depot and a Long-Acting SSA Device Across Related Attributes**

Note. Preference scale ranges from 1 (very poor) to 10 (excellent for the product attribute).
with metastatic disease, poorer prognosis, and symptoms related to increased tumor burden. In addition, the clinical course for these patients may be quite protracted and punctuated by heightened morbidity, frequent hospitalizations, and debilitating or embarrassing symptoms, such as diarrhea, excess flatulence, and flushing (Modlin et al., 2008; Oberg, 2012). The once-monthly dosing and administration protocol for lanreotide depot creates an opportunity for oncology nurses and patients to discuss symptom control and any adverse events that a patient may be experiencing, whether disease- or treatment-related. During these regularly scheduled encounters, nurses are well positioned to ensure continuity of care, provide patients with education on managing symptoms, monitor possible side effects, and assess HRQOL. The time savings with the prefilled syringes of lanreotide depot device may free time for these activities. In addition, oncology nurses who regularly administer injections to patients gain experience with drug-delivery modalities and techniques, ensuring doses are administered accurately and consistently across patient populations, regardless of body mass or thickness of subcutaneous fat. Reducing sources of error related to drug administration is one way to provide quality care in the clinic. A drug that combines improved PFS outcome, better control of disease symptoms, and is generally well-tolerated with a delivery system that instills confidence, is easy to use, and creates cost and time savings may have important implications for clinical practice. That said, additional studies in the setting of controlled clinical trials and real-world evidence should be undertaken to explore and validate these implications.

Conclusion

Lanreotide depot has been approved in the United States and in Europe based on improvement of PFS in patients with GEP-NETs (Ipsen Biopharmaceuticals, 2015). The antitumor effect of lanreotide depot on NETs has been demonstrated in phase II and phase III studies. Early treatment of this population may be significant in meeting the needs of patients with tumors that are detected at an early stage, a population that has shown a marked increase in incidence during the past 15 years (Hallet et al., 2014). Lanreotide depot has been generally well-tolerated in clinical studies and associated with few serious AEs (Alexopoulou et al., 2004; Caplin, Pavel, et al., 2014; Vinik et al., 2014). Patients have reported a high level of satisfaction in terms of symptom control, but there is a general lack of formal HRQOL assessments of patients with GEP-NETs receiving treatment with SSAs (Broder, Beenhouwer, Strosberg, Neary, & Cherepanov, 2015). Lanreotide depot, administered once monthly via deep subcutaneous injection, may be preferable compared with a long-acting SSA in patients who have difficulty tolerating an intramuscular injection. Subcutaneous injection may also be preferred for patients who are overweight or obese because excess body fat may interfere with proper intramuscular delivery (Boyd et al., 2013; Palma & Strohfus, 2013). In addition, patients with below-median body mass index, whose risk of progressive disease or death has been shown to be increased (Wolin et al., 2015), may be better served by subcutaneous administration. The attributes reported by nurses with respect to drug delivery, such as reduced time to administer the drug, lower incidence of clogging events, and more confidence that the dose was properly delivered, may translate to potential benefits to clinical practice, as well as cost savings that would be significant at the scale of population-based healthcare (Adelman et al., 2012; Marty et al., 2012). It is critical, however, that direct evidence through prospective studies be carried out to further explore and validate any association between site administration and device design and preferences among patients and oncology nurses.

References


